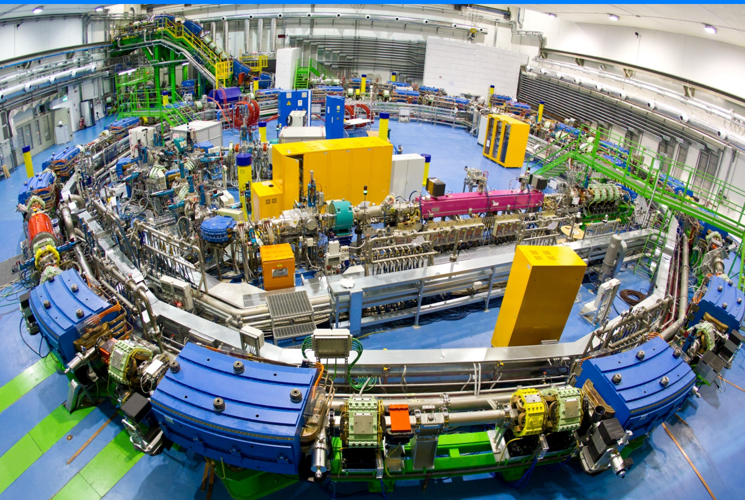
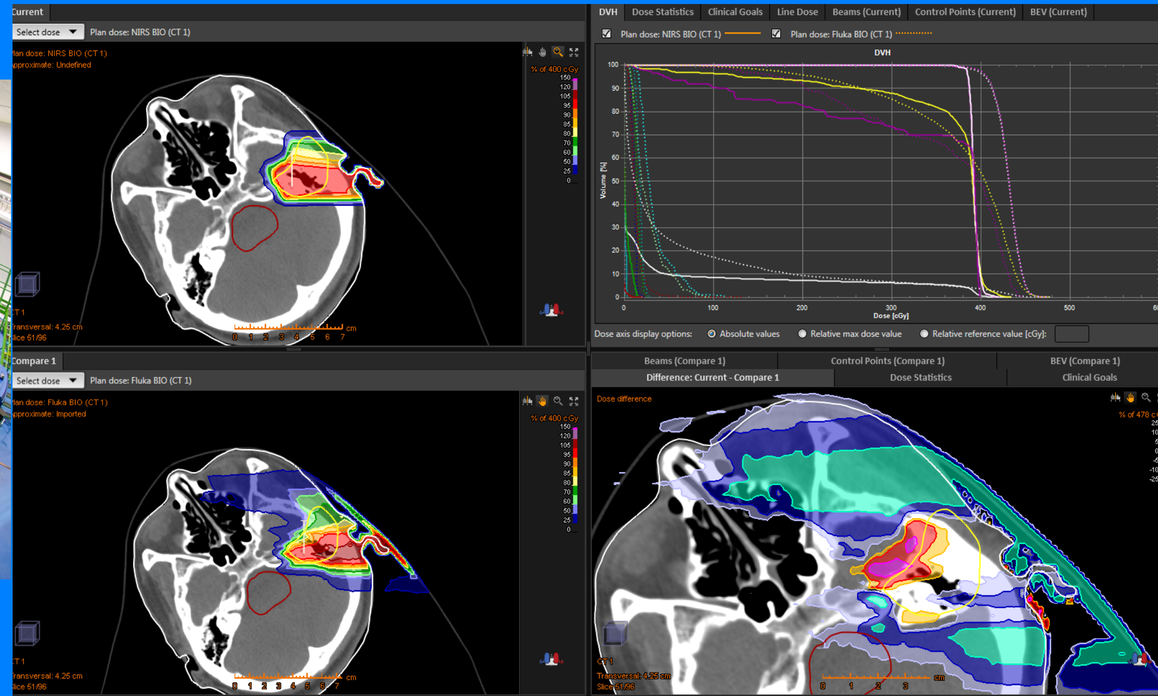




Introduction to Hadrontherapy

Giuseppe Battistoni,
INFN, Milano, Italy

ENLIGHT

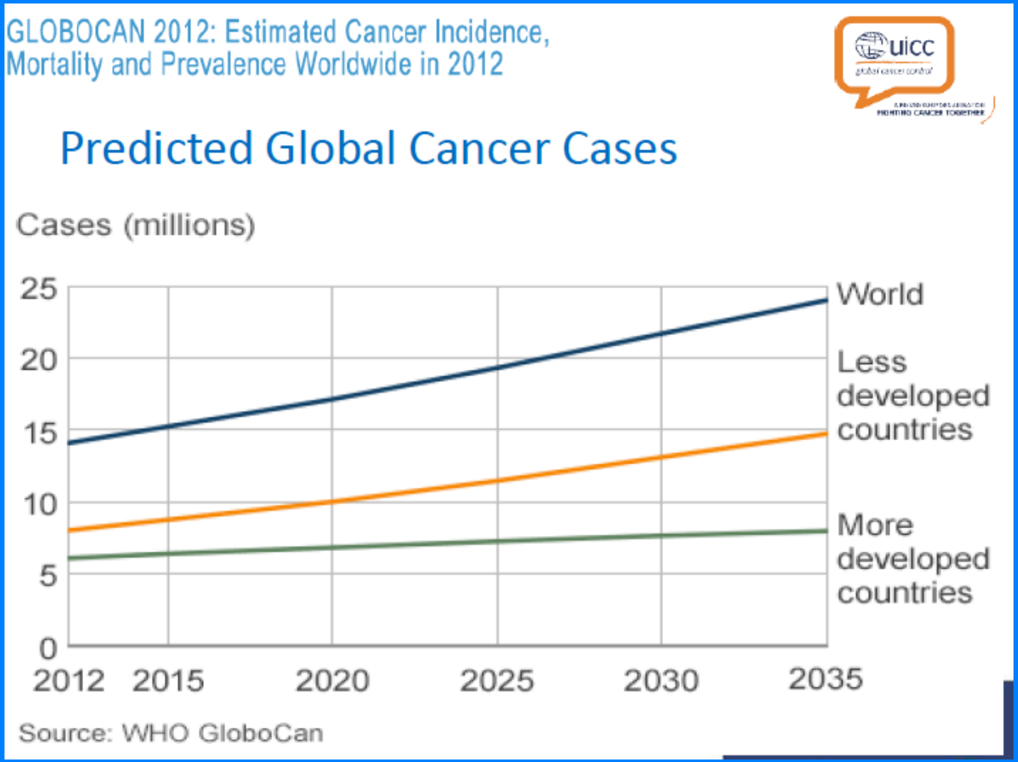
European Network for
Light Ion Hadron Therapy

INFN
Istituto Nazionale di Fisica Nucleare

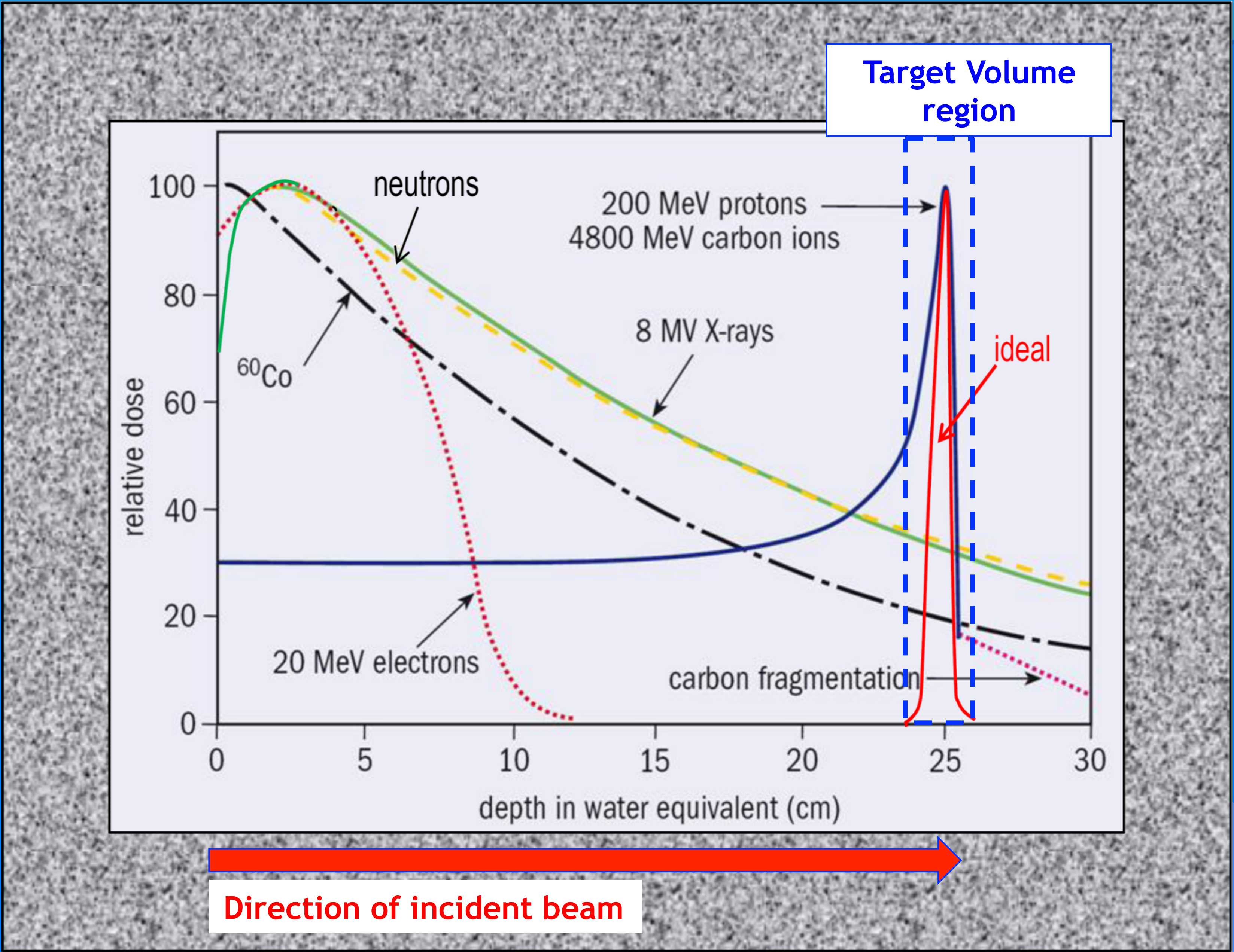
Why Cancer and Physics Technologies?

Cancer a large and a growing societal challenge:

- **More than 3 million new cancer cases in Europe**
- **Nearly 15 million globally in 2015**
- **This number will increase to 25 million in 2030**
- **Currently around 8 million deaths per year**



Motivation of Charged Particle Therapy



History of Hadrontherapy: some milestones

1945, R. Wilson: first proposal to use hadrons for radiotherapy

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

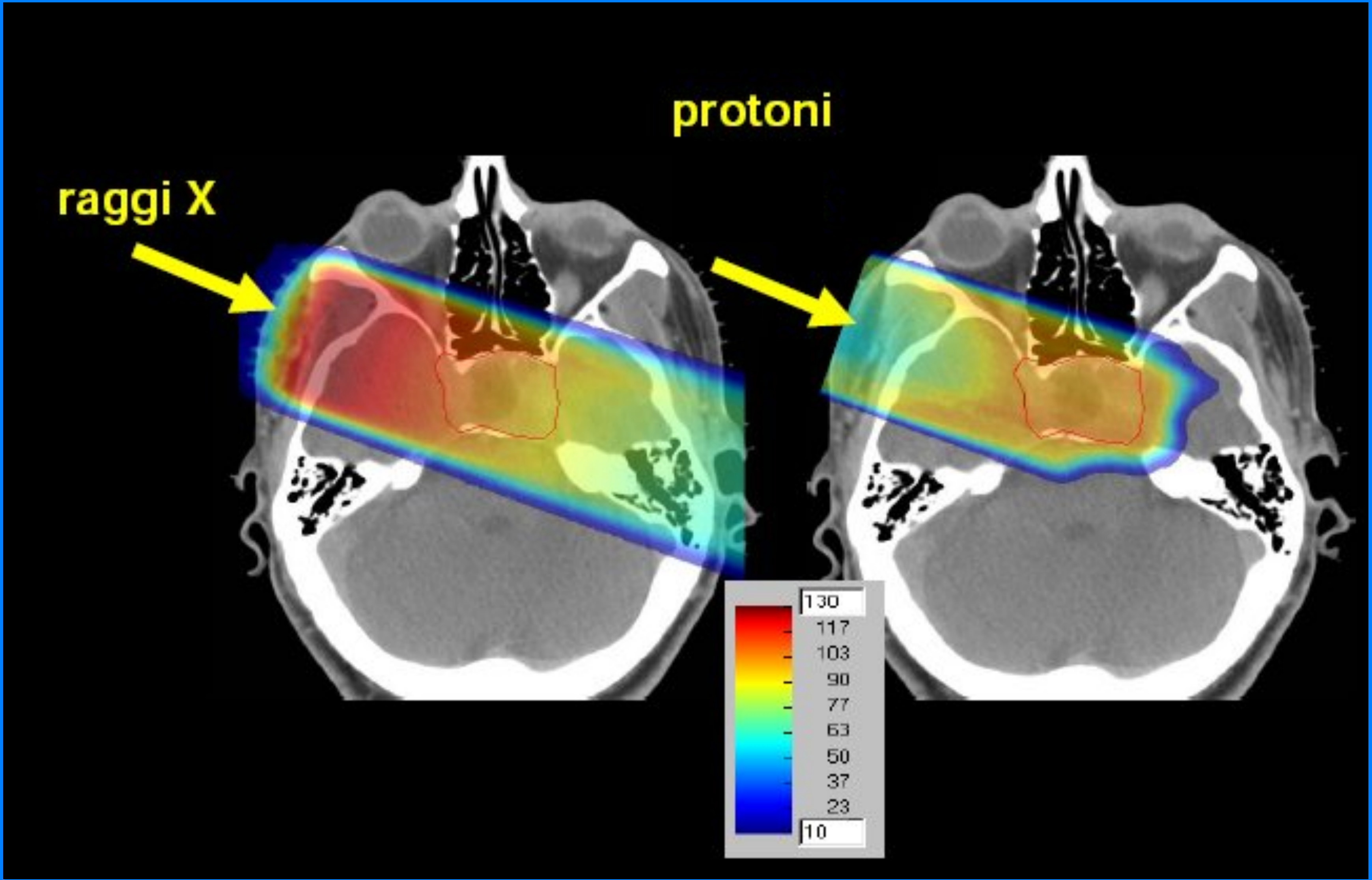
EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles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

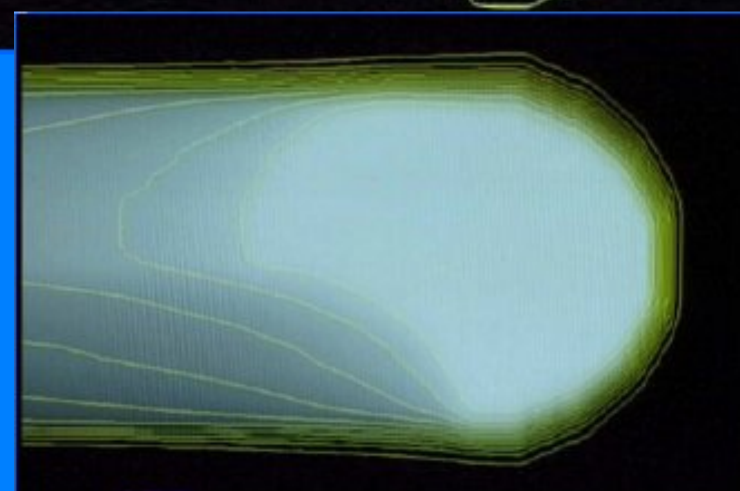
Radiology 47: 487-491, 1946

1954 - Berkeley treats the fi rst 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 fi rst 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


protoni
raggi X
130
117
103
90
77
63
50
37
23
10

Conformation capability

~250 MeV
protons

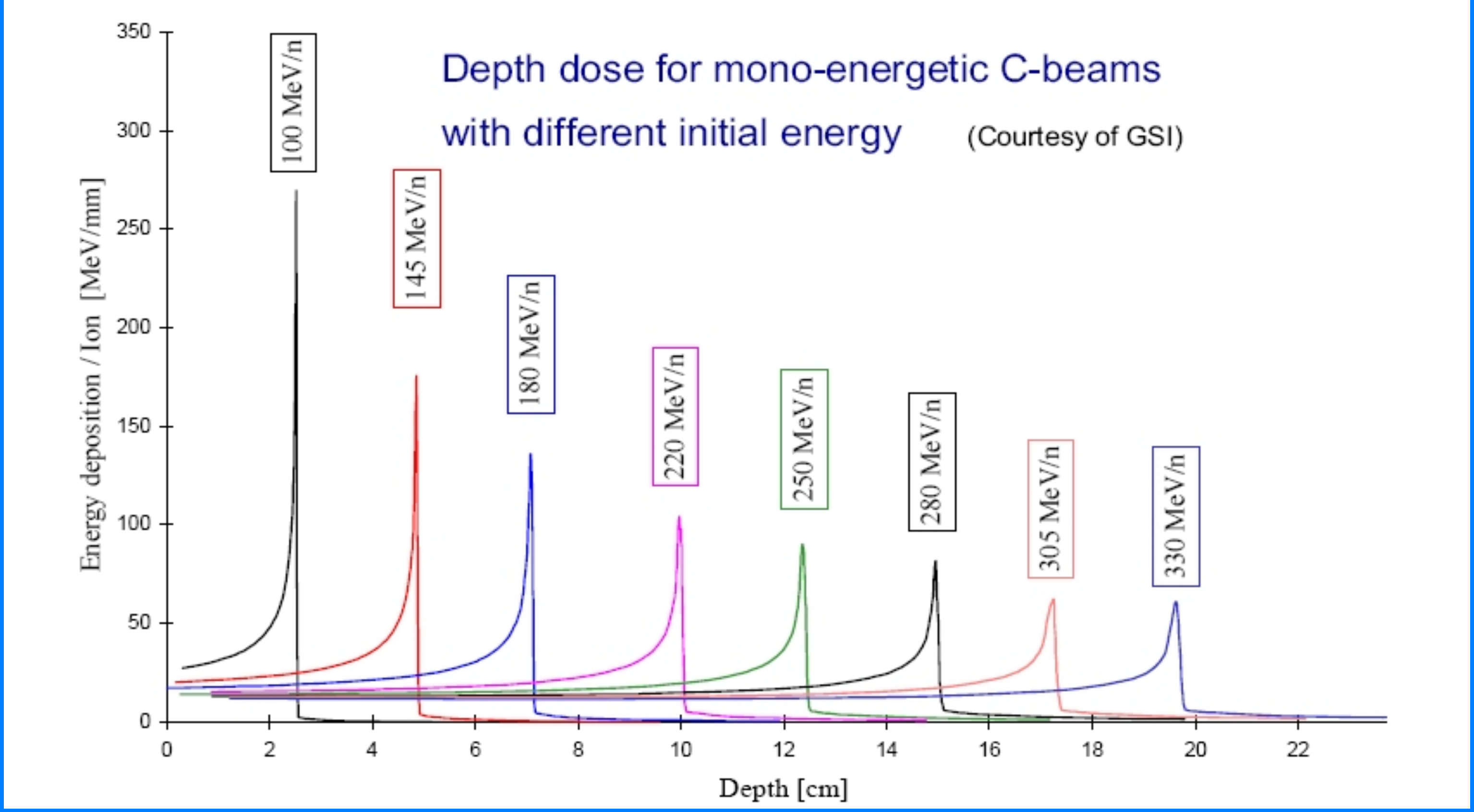


muovendo il fascio in X,Y e
variandone l'energia (profondità raggiunta)

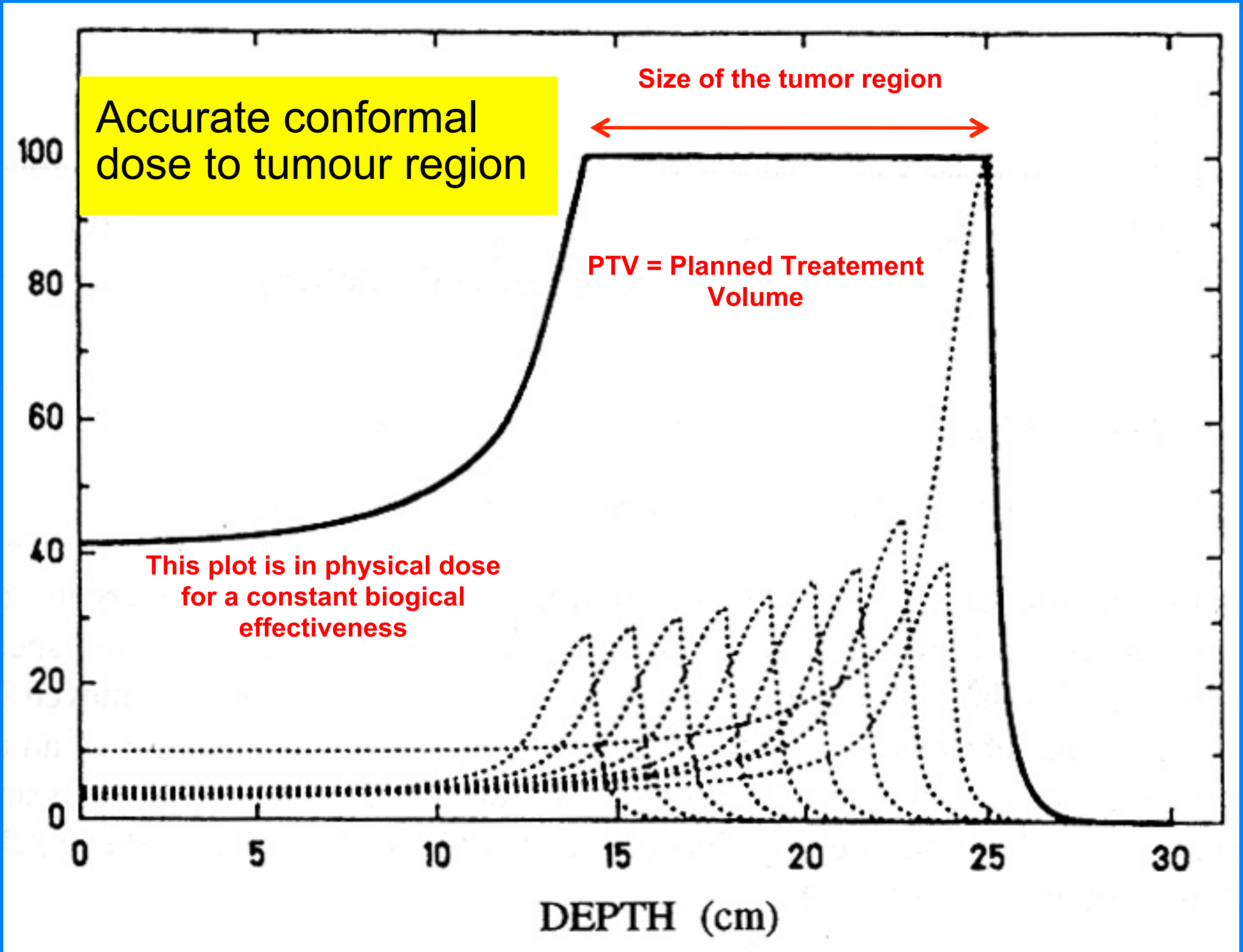
tutto il bersaglio puo' essere efficacemente irradiato

Energy – Depth Correlation

Beams with Different Energy deposit energy at Different Depths
→ dose modulated along the beam direction

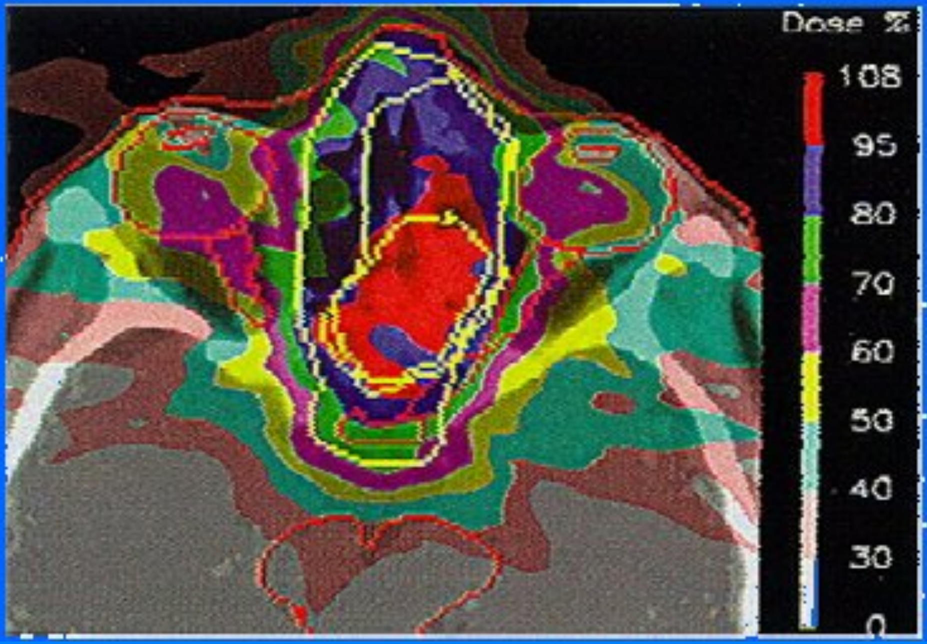


Conformation: the concept of Spread Out Bragg Peak (SOBP)

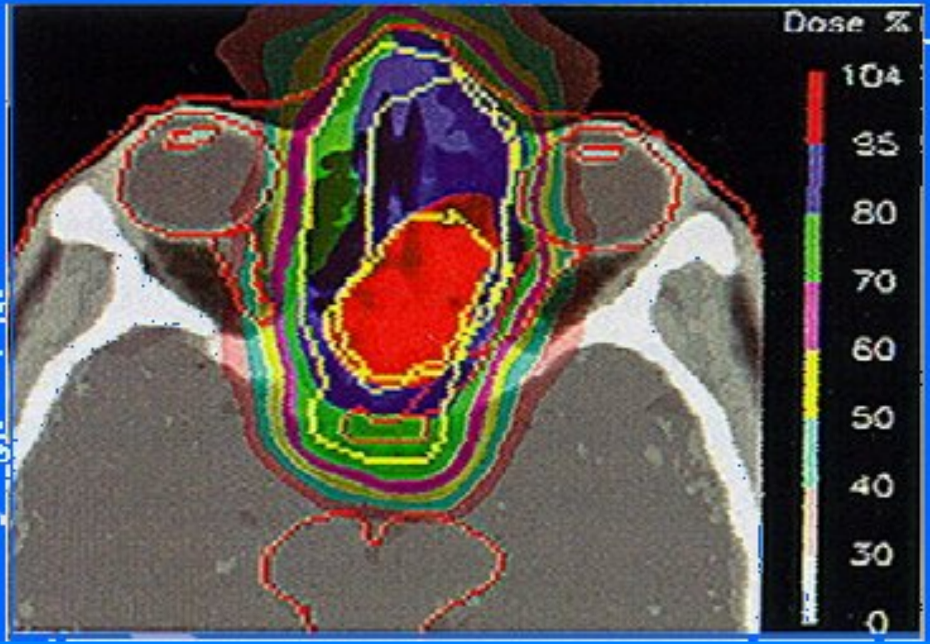


Comparing photon and proton therapy

9 X-ray beams

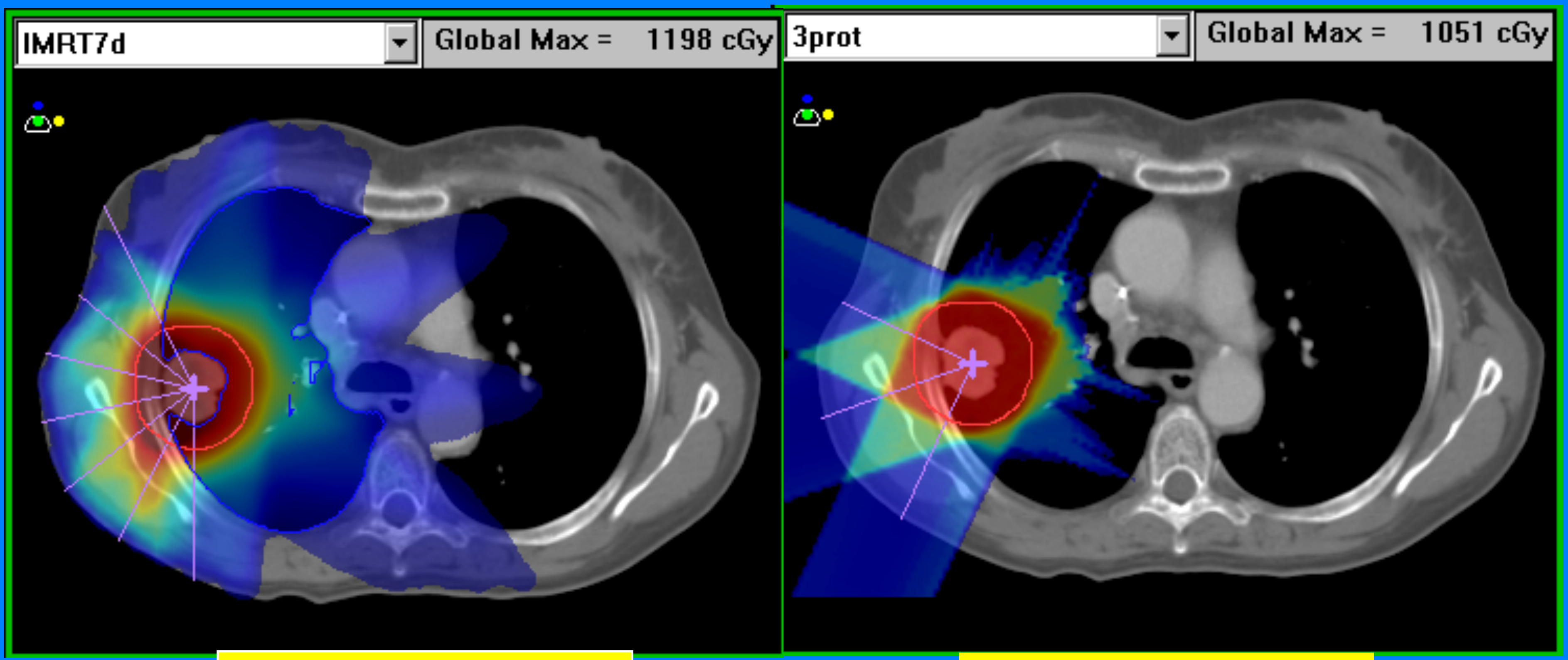


a single proton beam



(Courtesy of Prof. U.Amaldi)

Comparing photon and proton therapy



IMRT

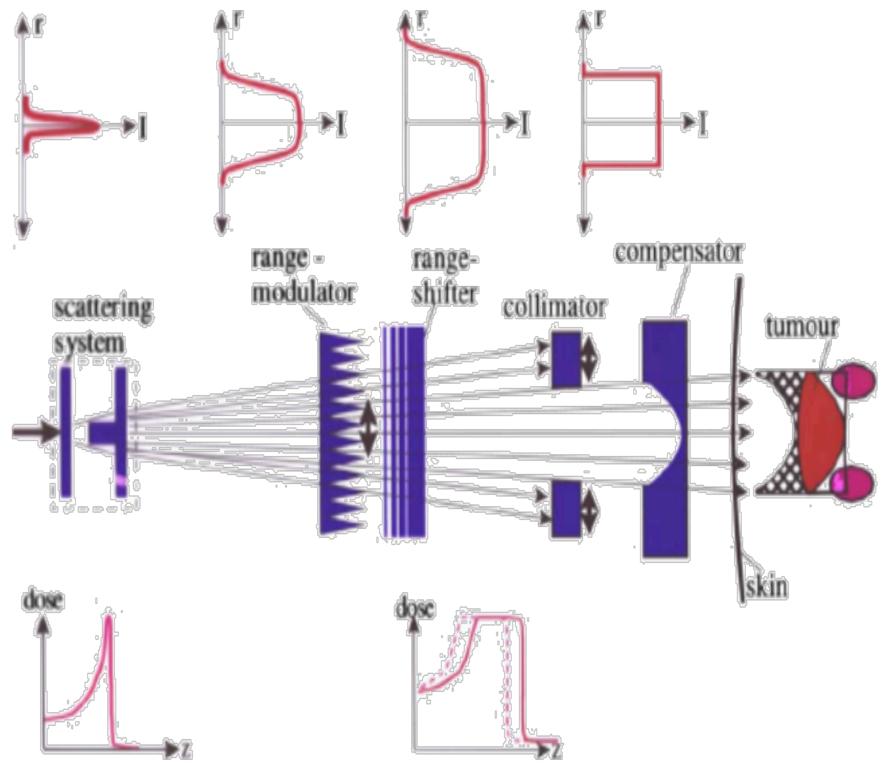
Hadrontherapy

Advantage of hadrontherapy stays mostly in selectivity power:

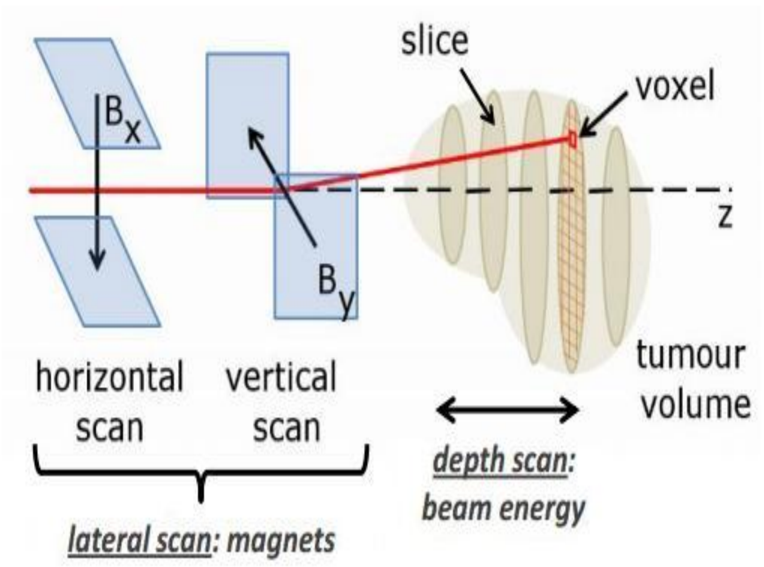
- better capability to spare Healthy Tissues and Organs at Risk, for the same dose.
- Not necessarily there is a clear advantage in the Rumor Control Probability (for the same dose)

Treatment Delivery

Passive delivery



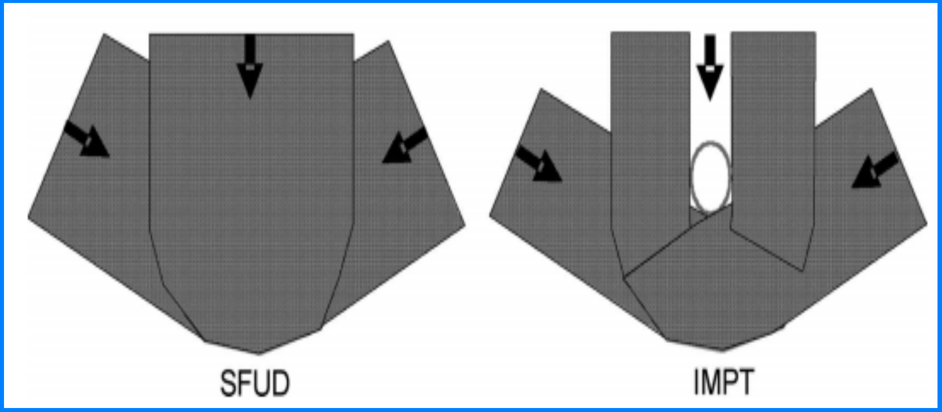
Active delivery



Proton Therapy: Scanning Beams

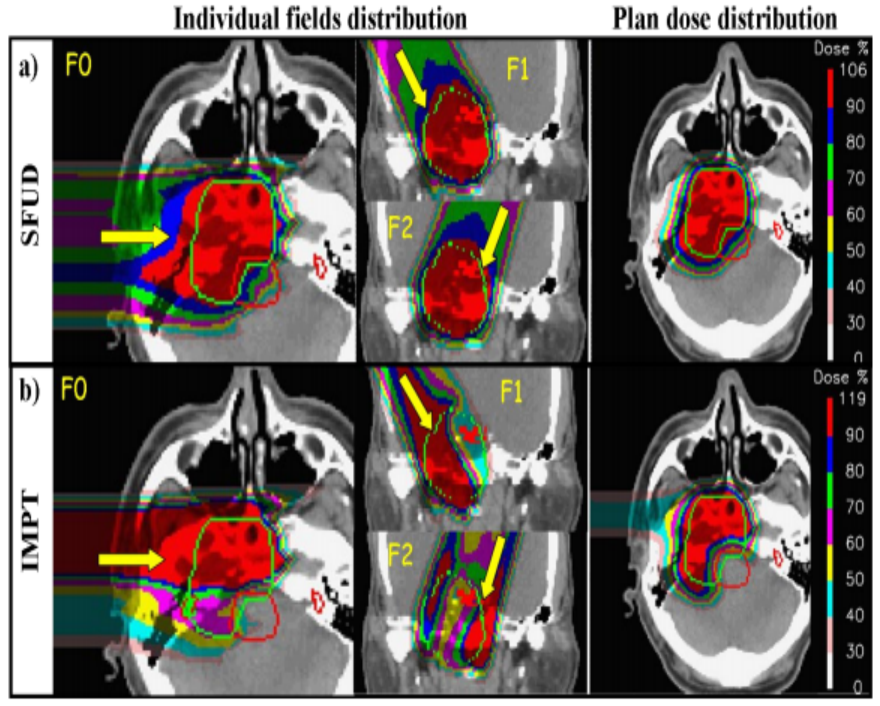
Single Field Uniform Dose (SFUD)

Combination of individually optimised fields, each of which deliver a homogenous dose across the target



Multi Field Optimisation (MFO) or Intensity Modulated Proton Therapy (IMPT)

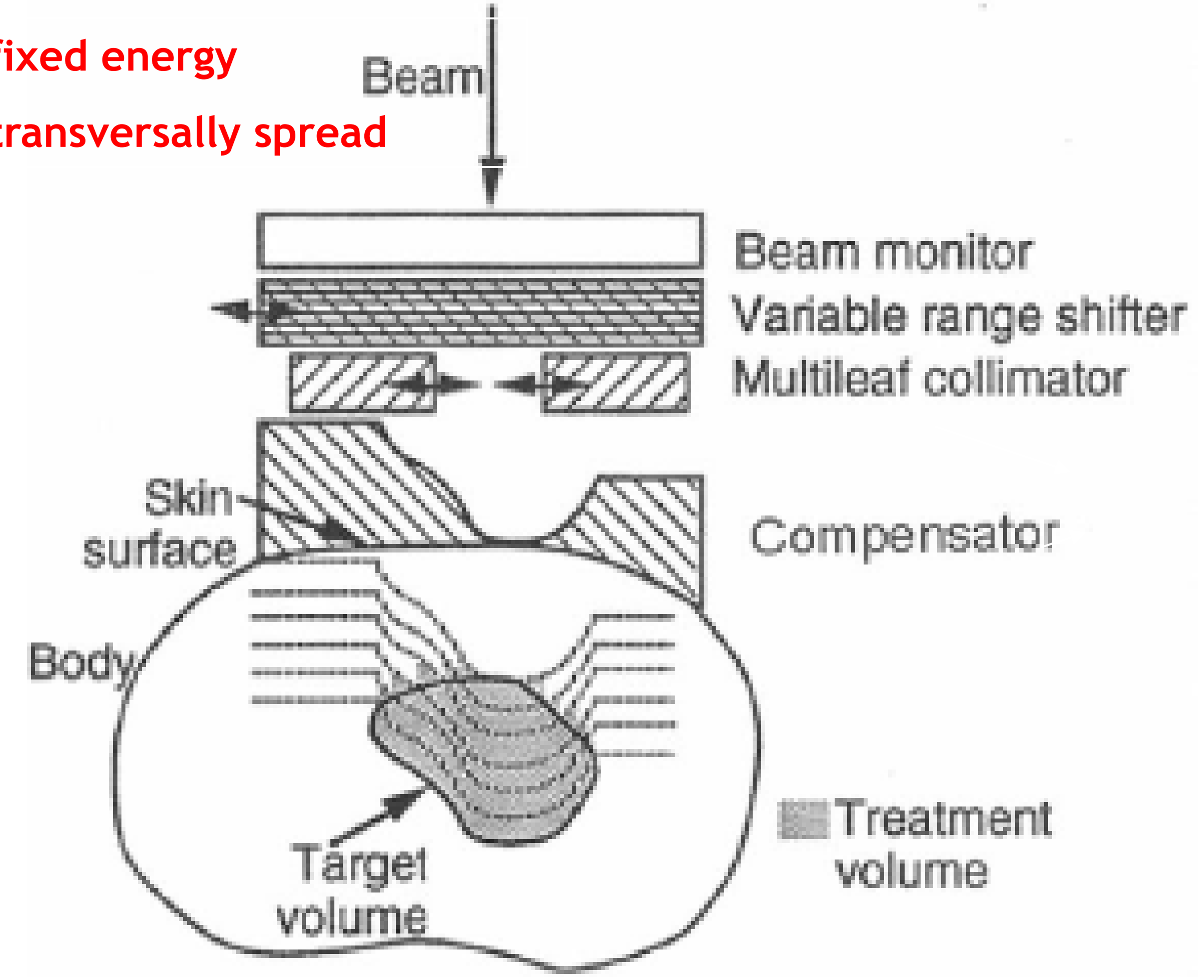
Simultaneous optimisation of all Bragg peaks from all fields: the sum of the beams covers the target uniformly with dose. It provides more degree of freedom and better normal tissue sparing, especially for OARs on the proximal side of the target.



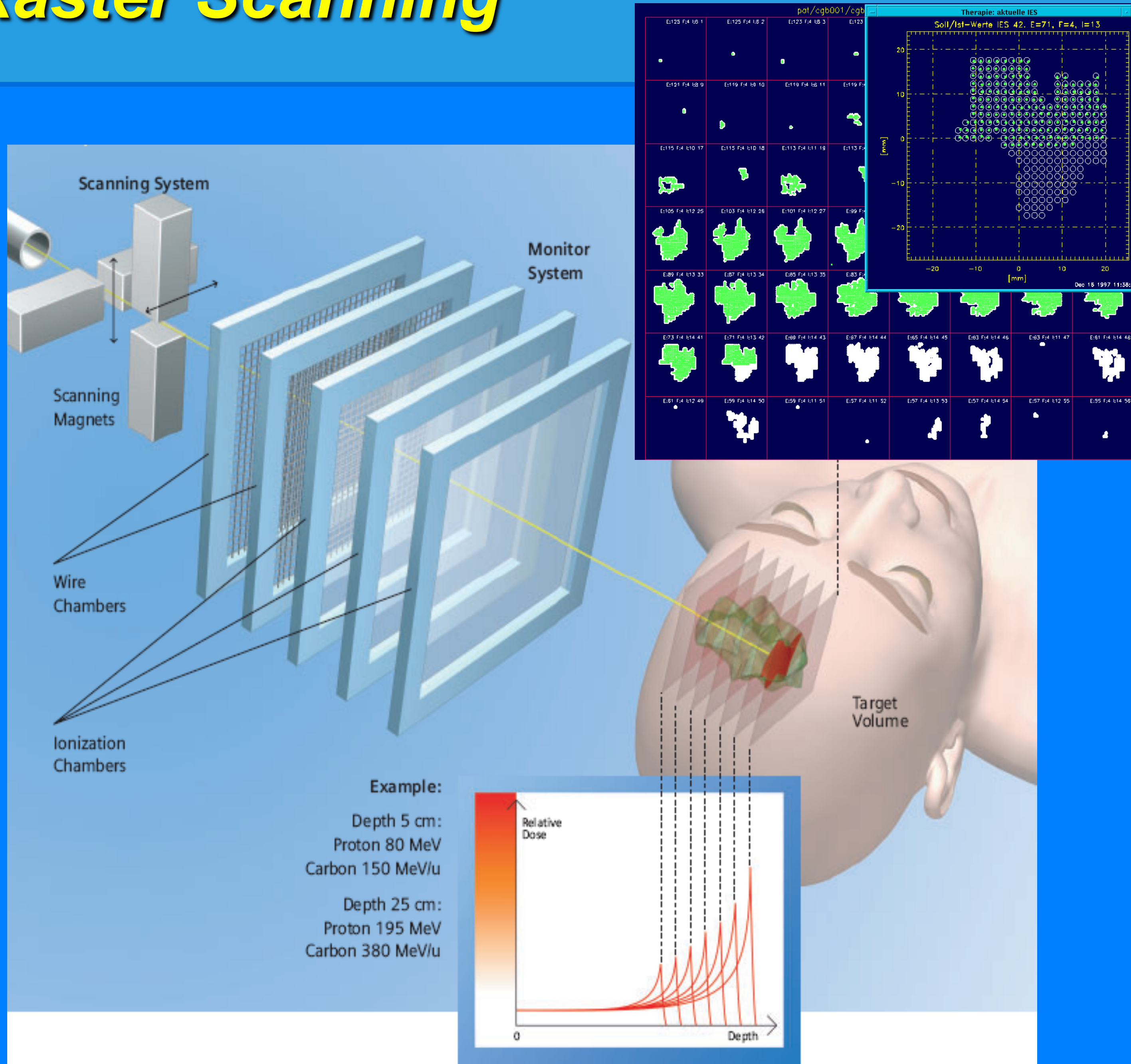
Passive Treatment Modality

fixed energy

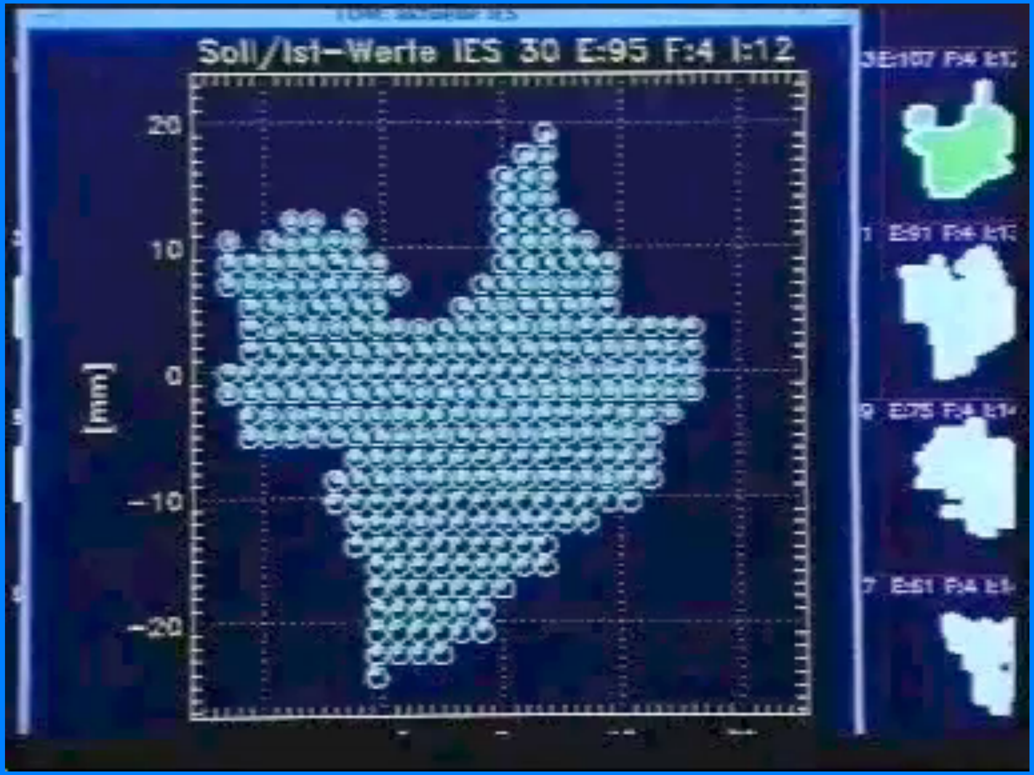
transversally spread



Active Raster Scanning



Active Raster Scanning



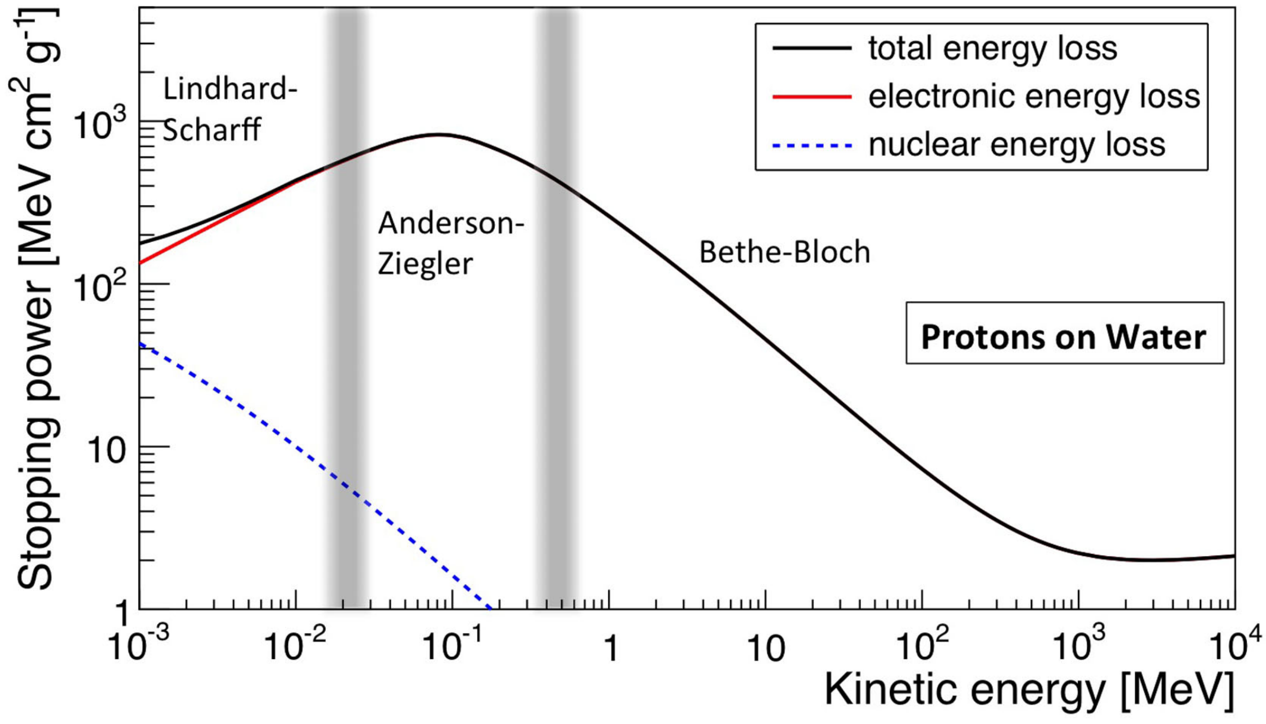
Physics of Bragg Peak

important at Low Energy dE/dx:

- Shell Corrections

High order corrections

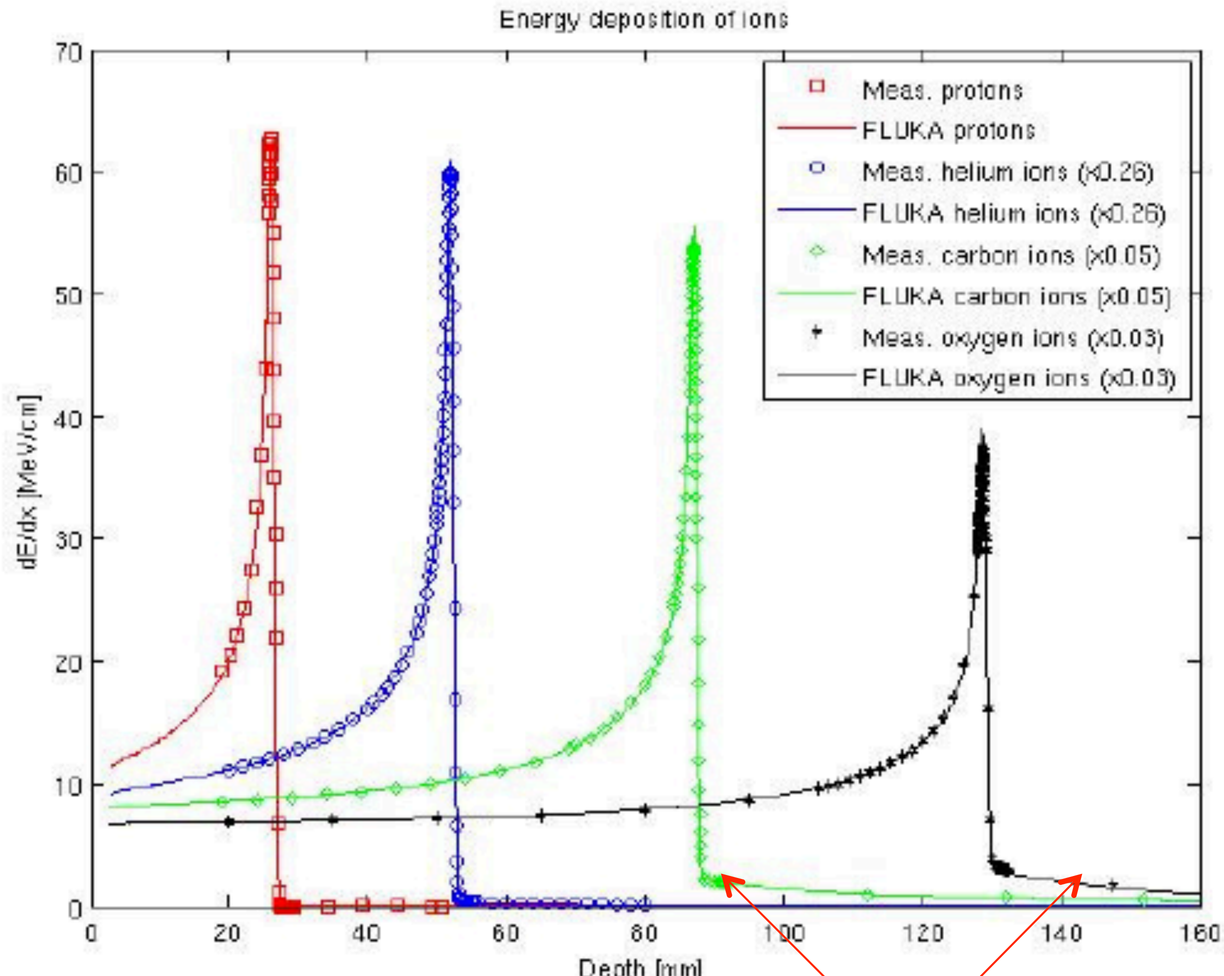
- Barkas correction ($\propto z^3$)
- Bloch correction ($\propto z^4$)
- Mott corrections

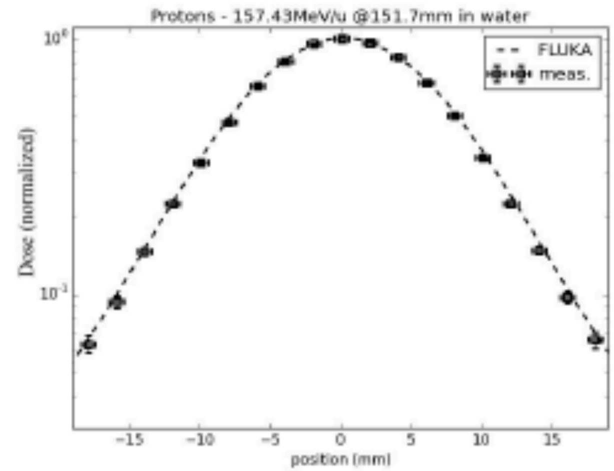


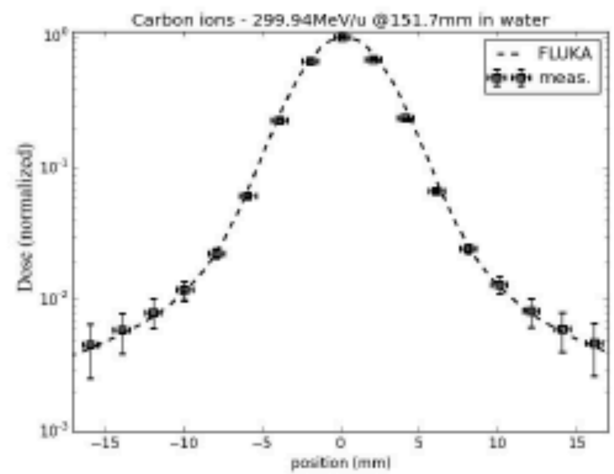
dominated by
interaction with electrons

MCS, Energy loss fluctuations
and nuclear interactions
do affect the shape!

Bragg Peak Physics



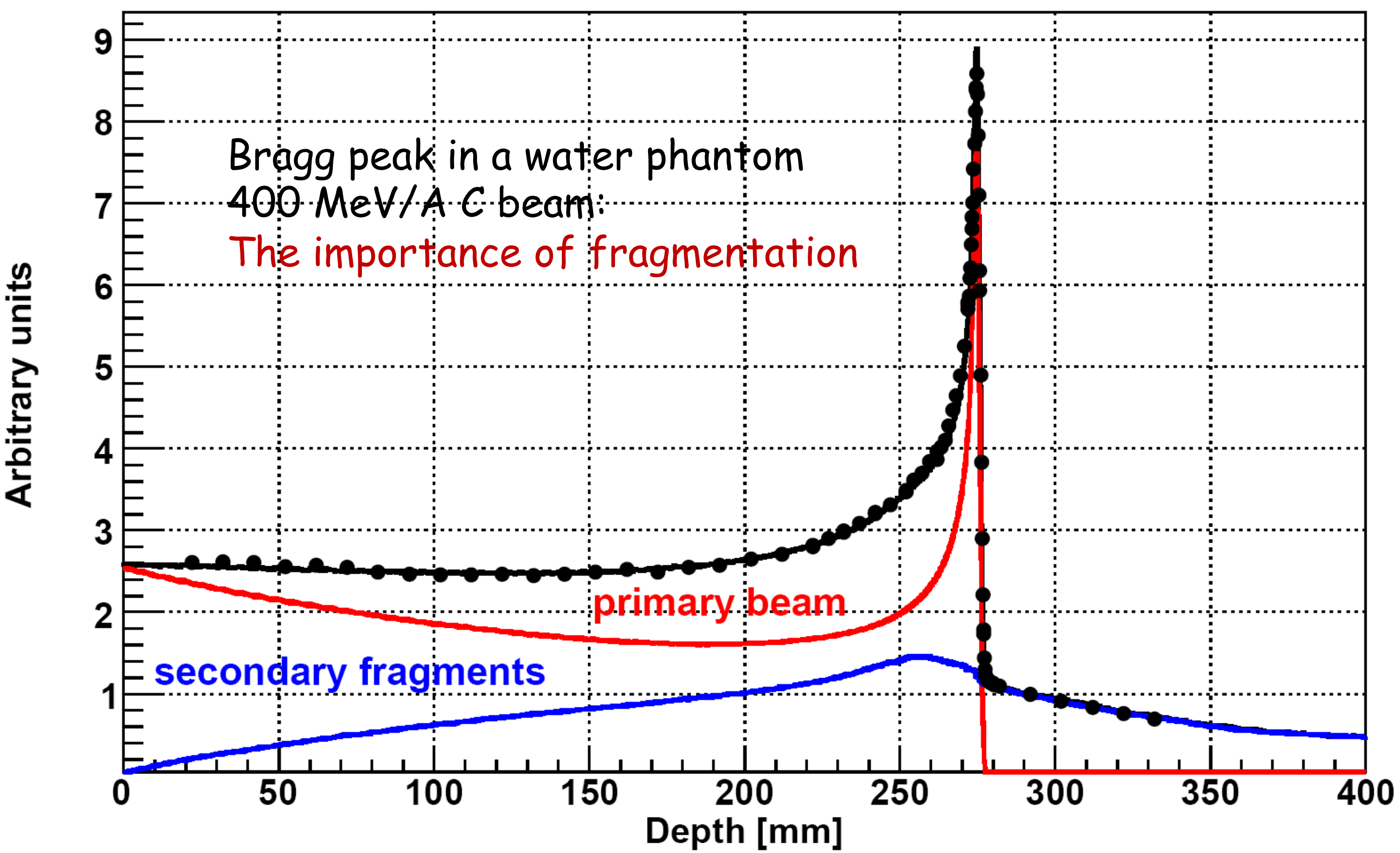




Some apparently trivial parameter is not well known. For example: <I>

Tail beyond the Peak due to nuclear fragmentation of Projectile

Hadrontherapy with nuclei: Ion Therapy



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

Interdisciplinary aspects: Physics and Biology

Ionisation tracks

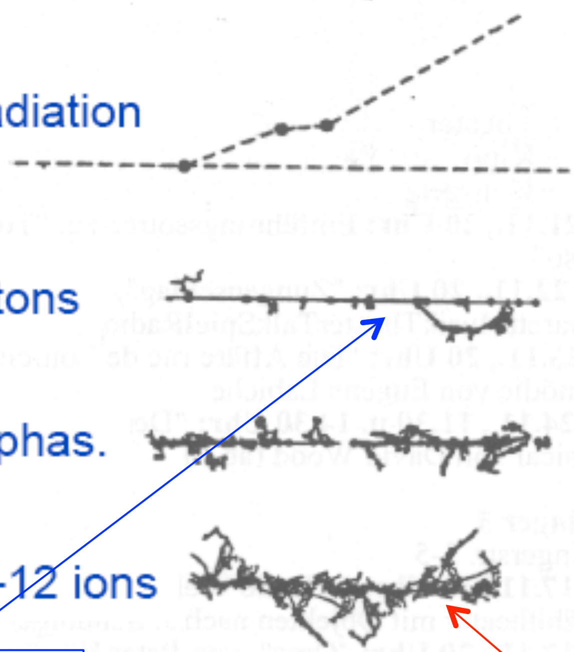
LET

Gamma radiation

1MeV Protons

1MeV/u alphas.

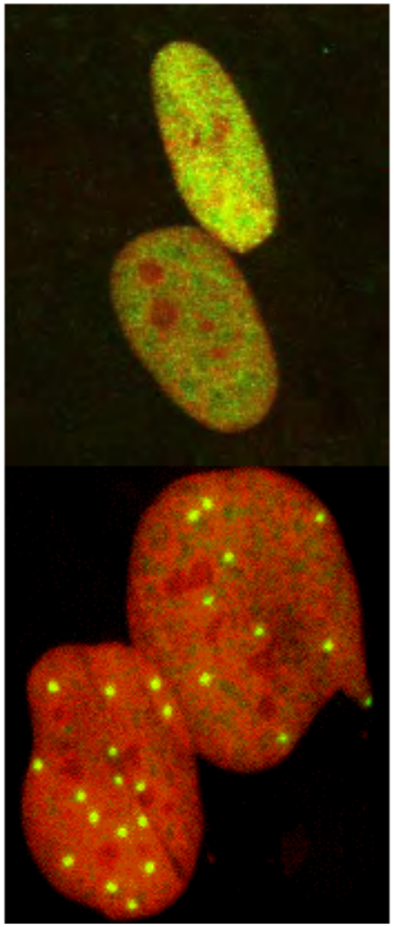
1MeV/u C-12 ions



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



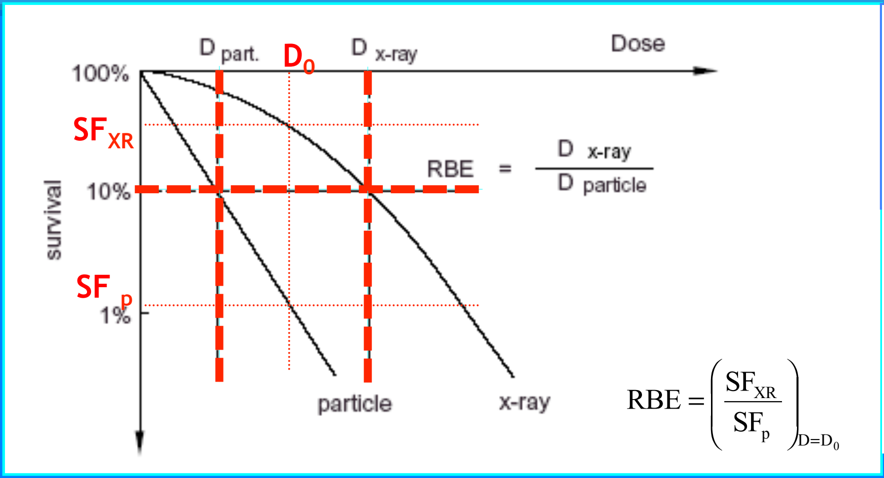
Low LET

Homogeneous deposition of dose

High LET

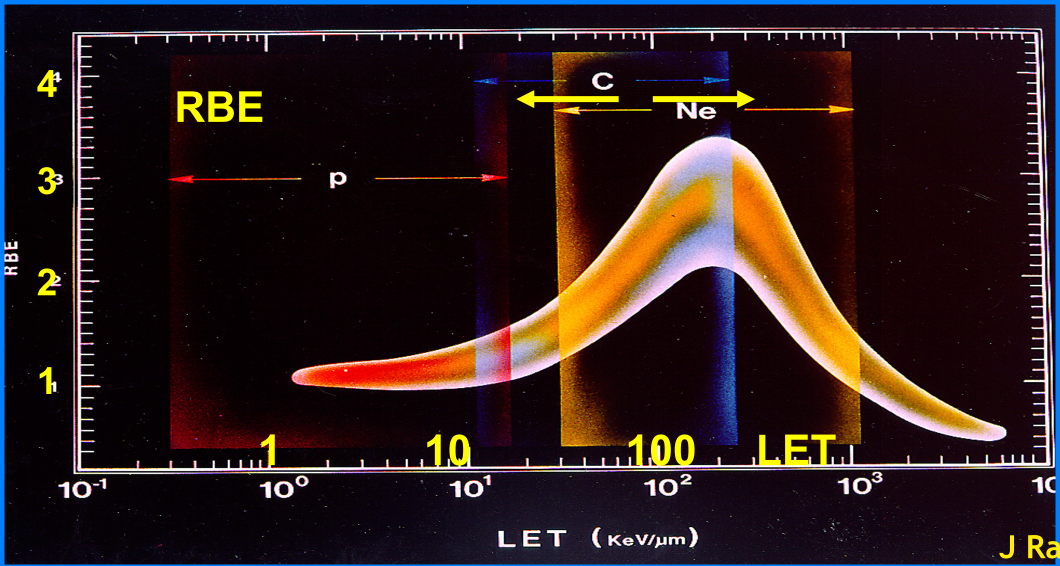
Local deposition of high doses

Radio Biological Effectiveness (RBE) and Oxygen Enhancement Ratio (OER)



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

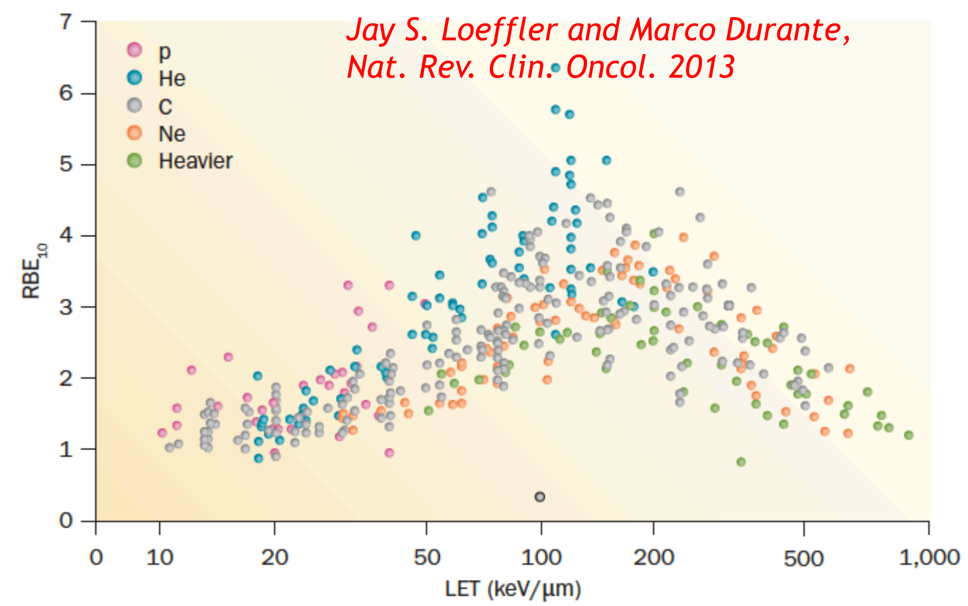
for a given type of biological end-point and its level of expression.
For example:
Survival Fraction of 10%



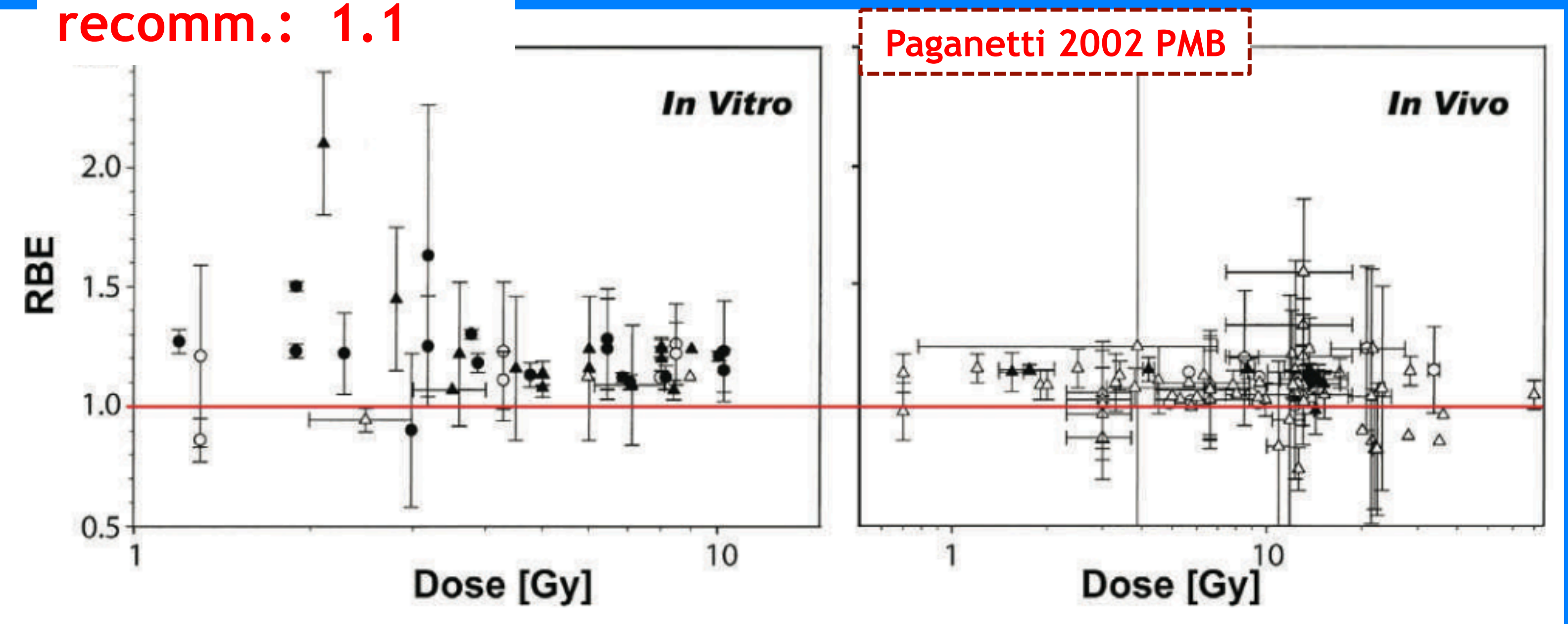
J Radiat Res. 2014 Sep; 55(5): 902-911.

Radiobiology and its uncertainties

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



RBE of protons
recomm.: 1.1

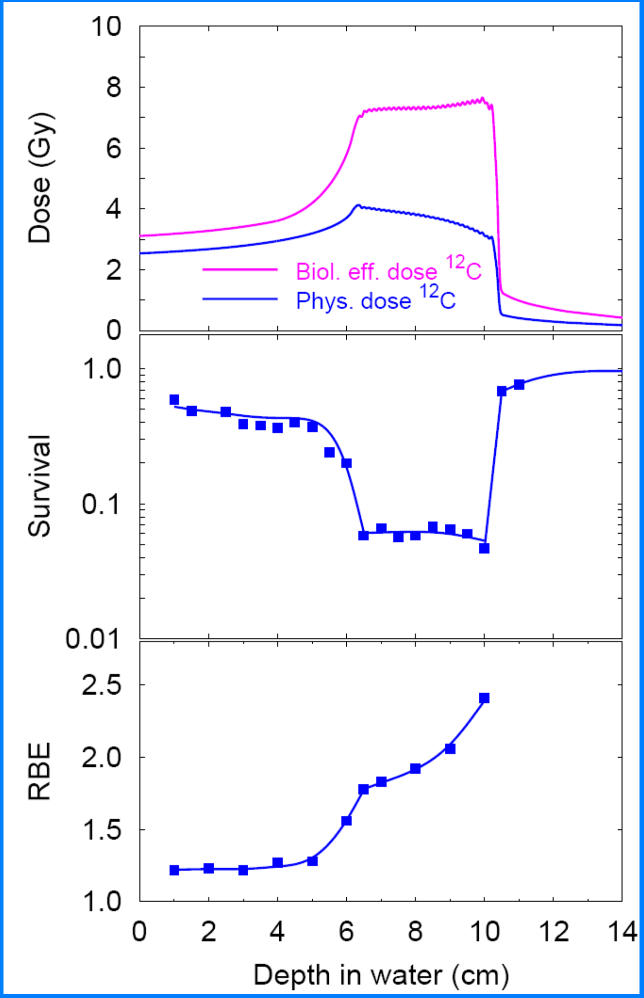


New Paradigm for Proton Radiobiology (Girdhani 2013 Radiat Res) → **Protons and photons present distinct physics and biological properties at Sub-Cellular, Cellular and Tissue level**

Nuclear projectiles in Particle Therapy today

protons: 50-250 MeV

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

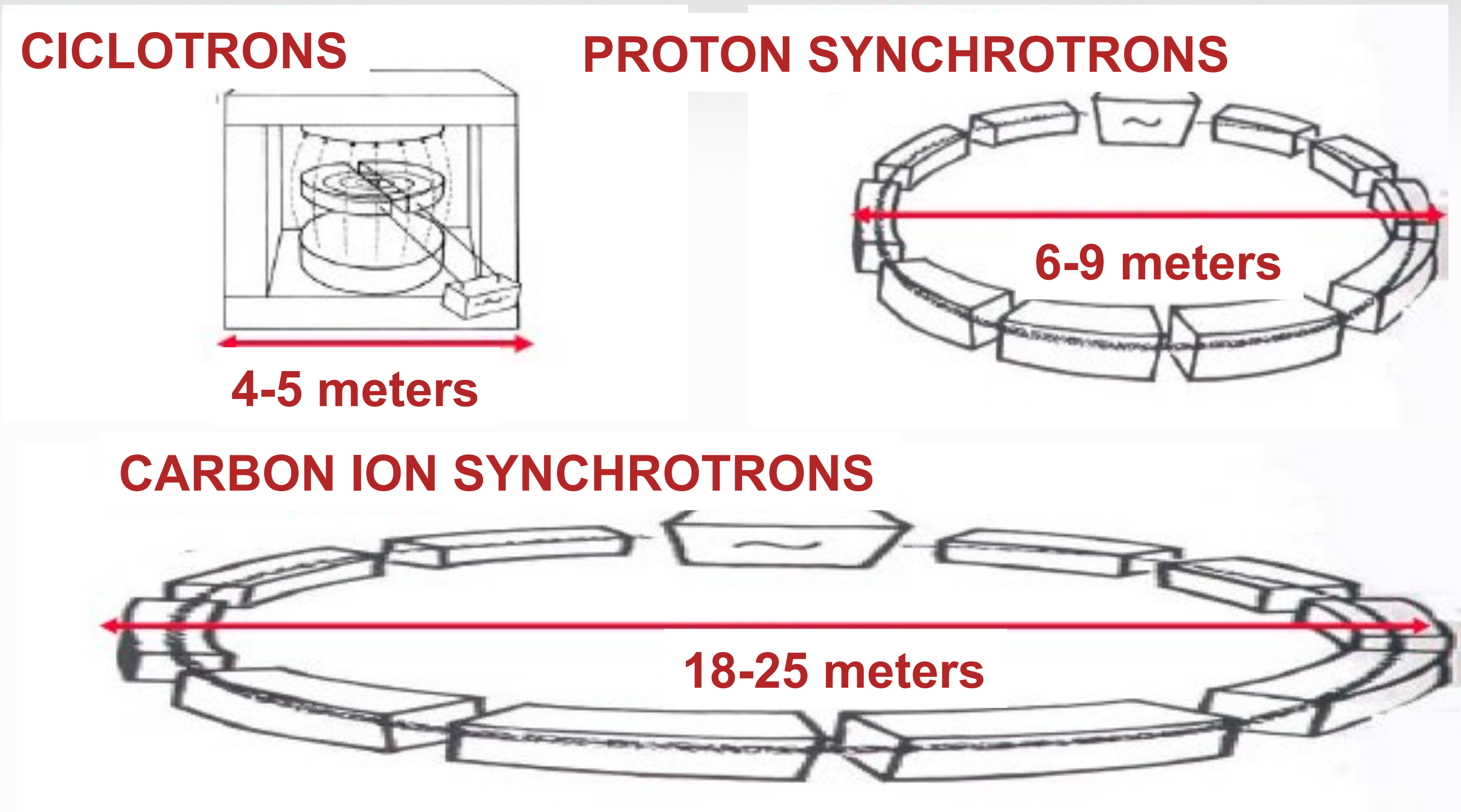


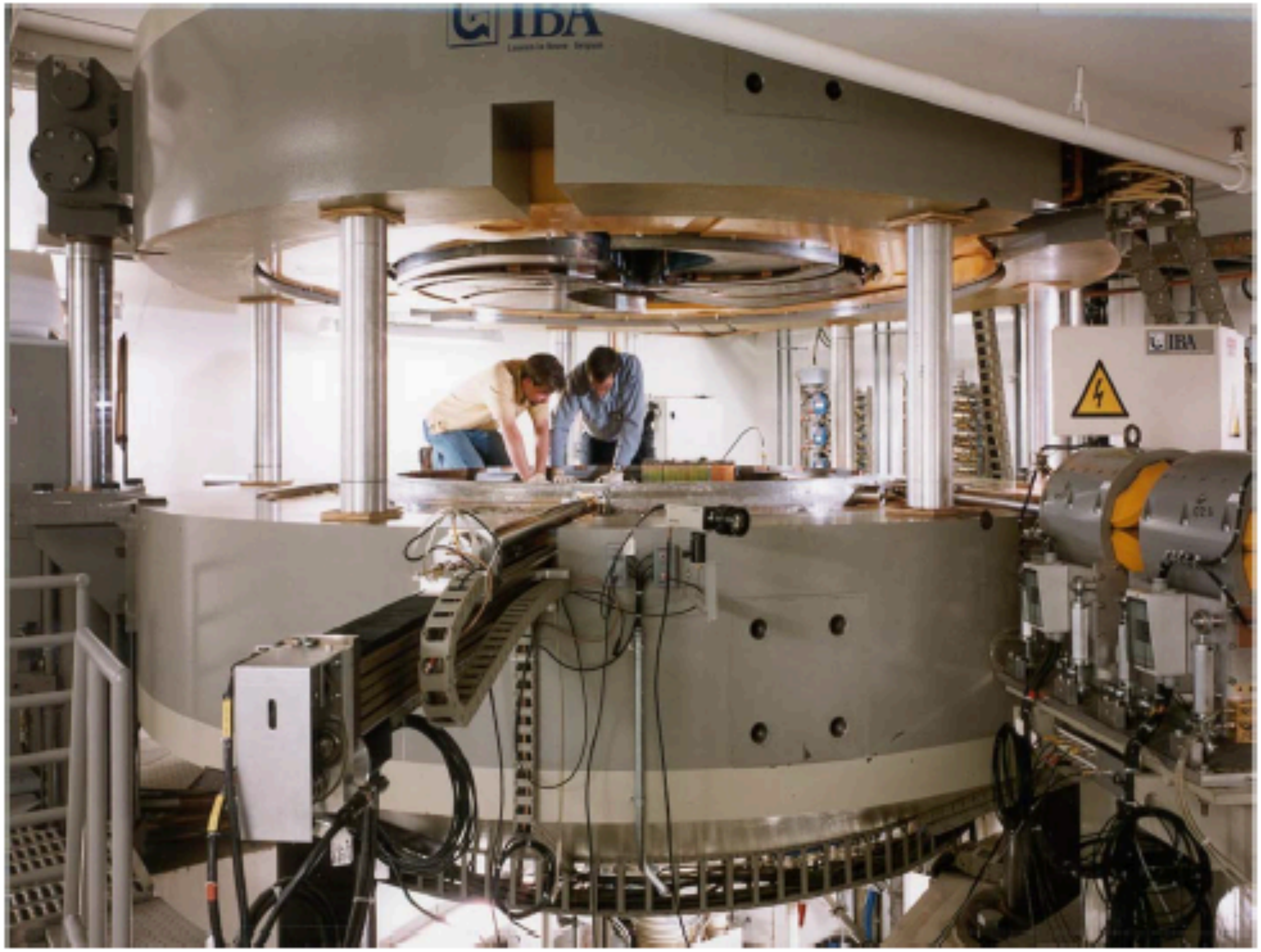
^{12}C: 60-400 MeV/u

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

However:
variable RBE vs energy, LET, …
accelerated by larger machines
Nuclear Fragmentation (➔complex RBE)
heavier gantries and magnets…

Cyclotrons or Synchrotrons





IBA
Varian
Sumitomo
ProNova
Etc…

The IBA 235 MeV Room temperature Cyclotron (230 tons)

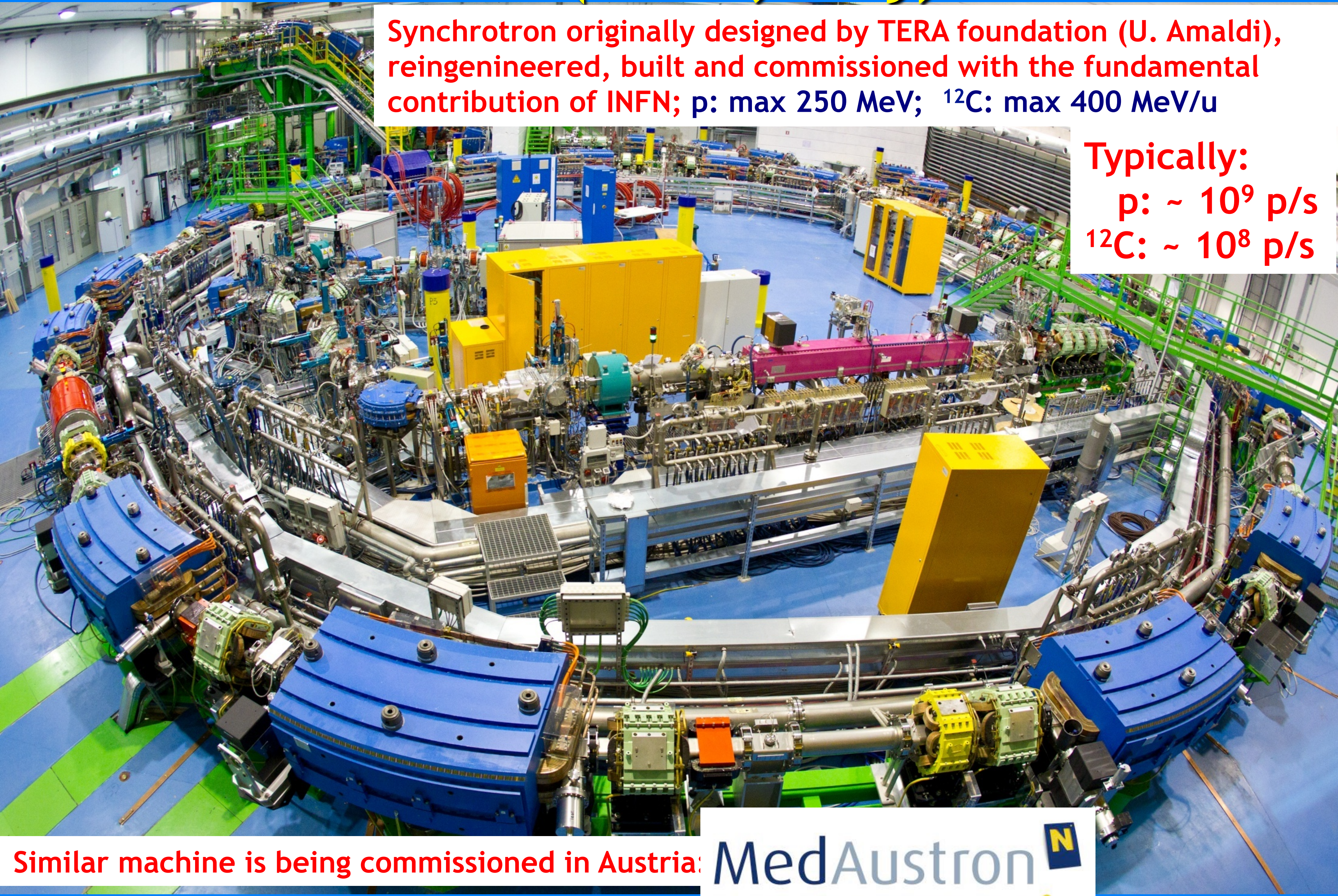
CNAO (Pavia, Italy)

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

Typically:

p: ~ 10^9 p/s

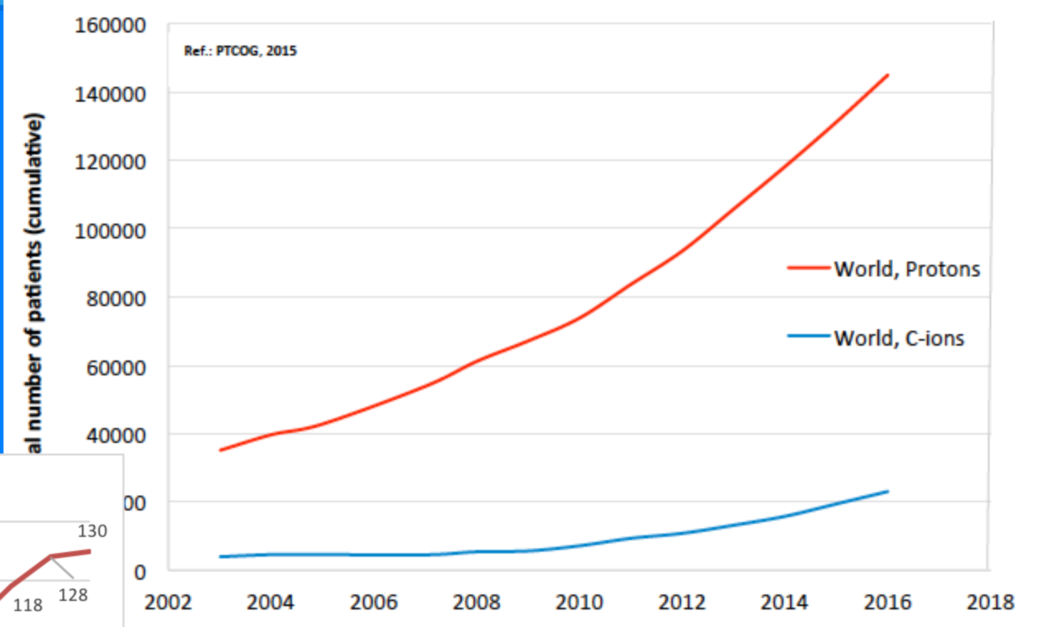
^{12}C: ~ 10^8 p/s

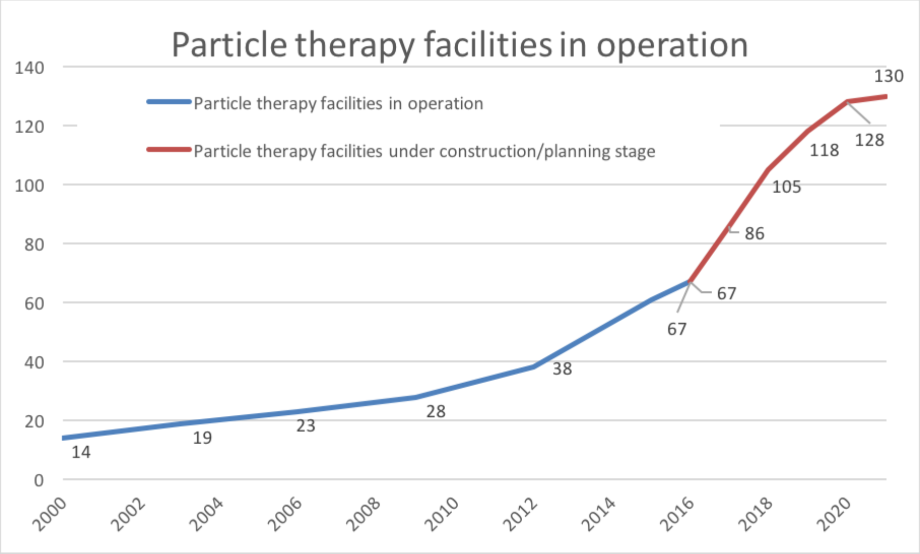


Similar machine is being commissioned in Austria: MedAustron

Patient Statistics 2016 (www.ptcog.ch)

He	2054	1957-1992
Pions	1100	1974-1994
C-ions	21580	1994-2016
Other ions	433	1975-1992
Protons	149345	1954-2016
Grand Total	174512	1954-2016





In 2014, about 10% of patients were pediatric and another 10% were treated for ocular melanomas.

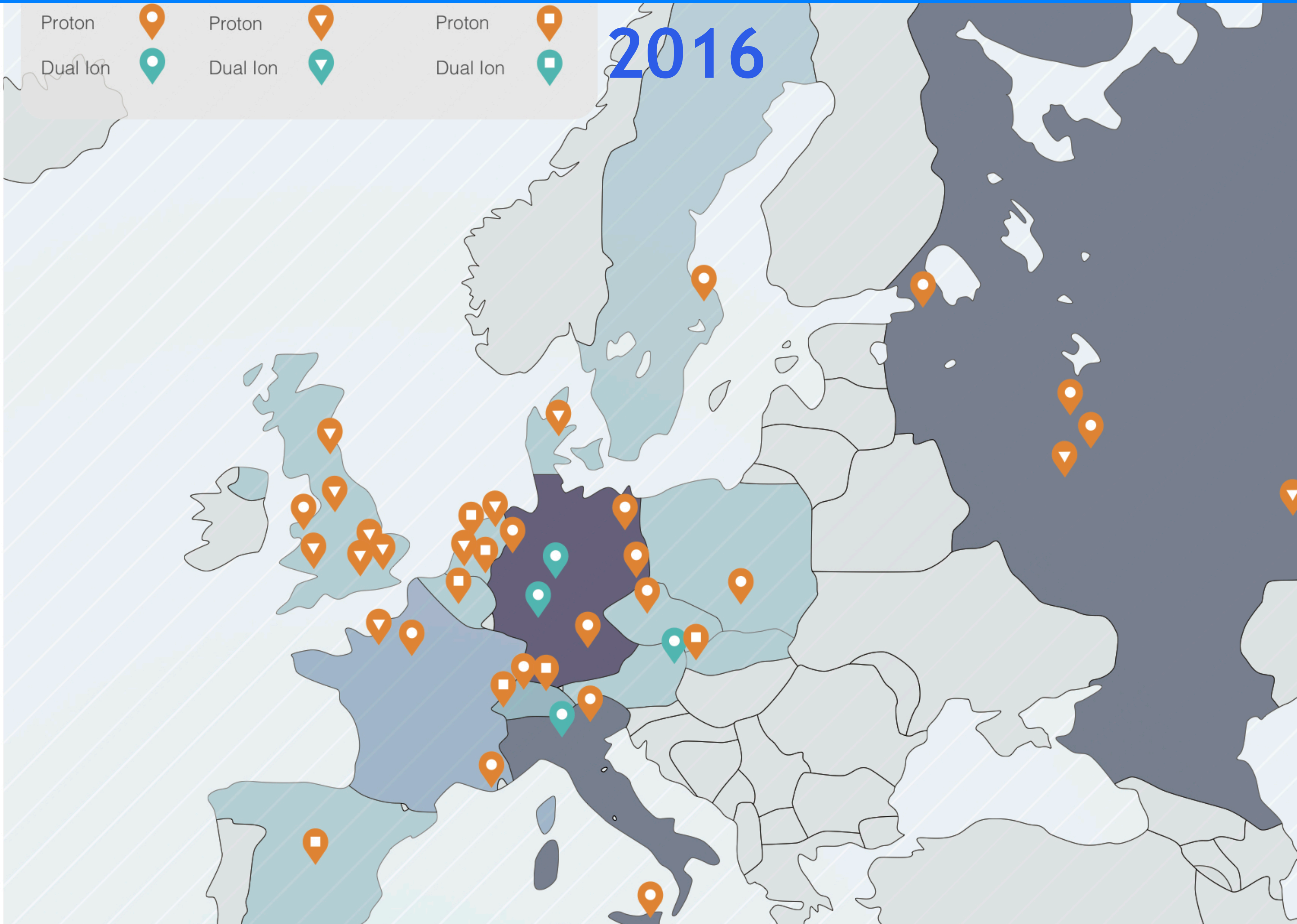
Particle therapy centres in Europe - 2002

P centres

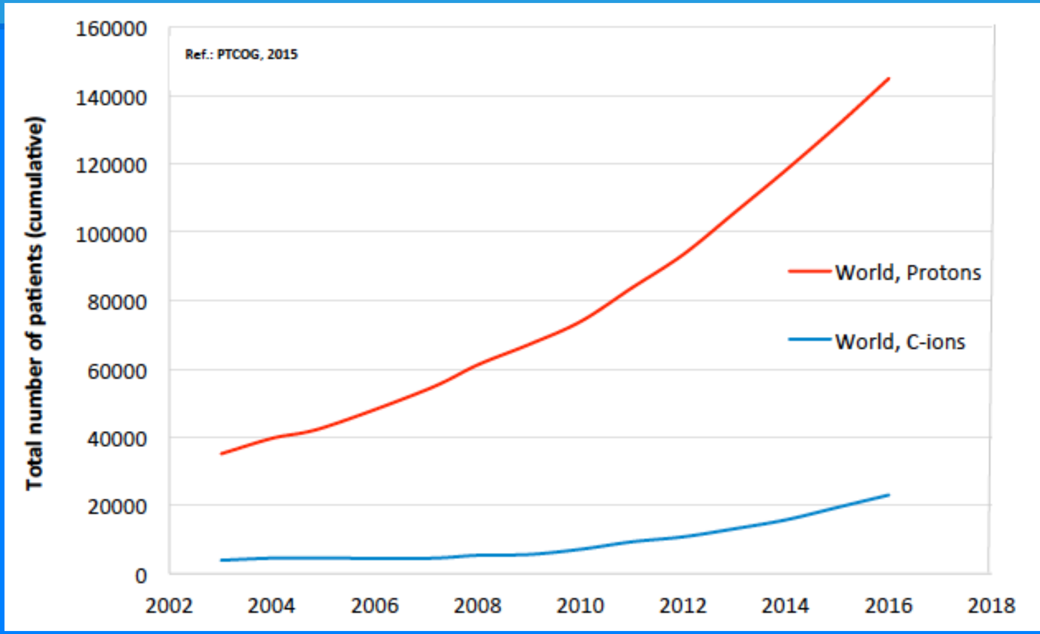
C-ion centres

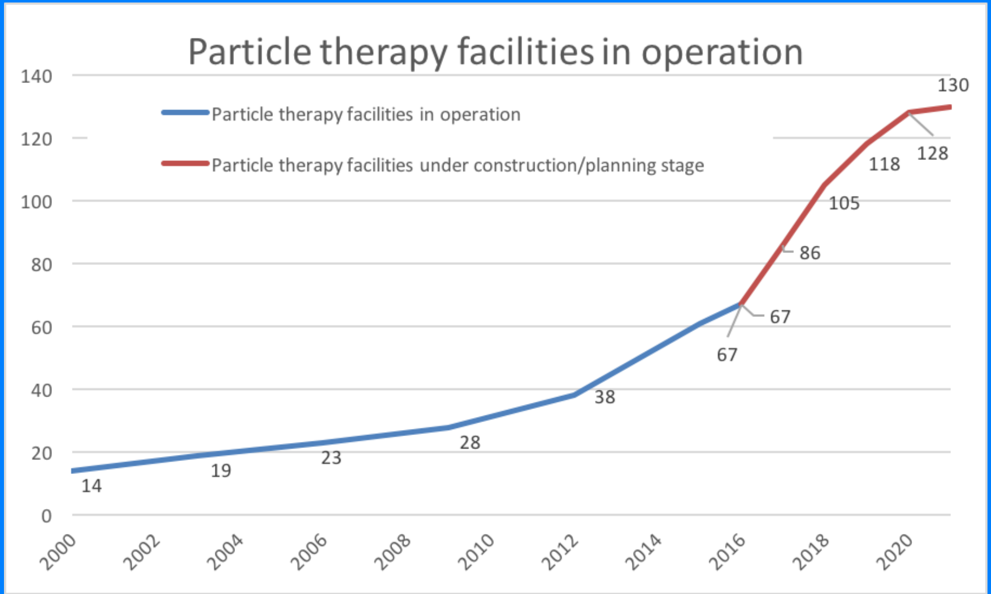
Source: PTCOG, October 2015

Particle therapy centres in Europe - 2016



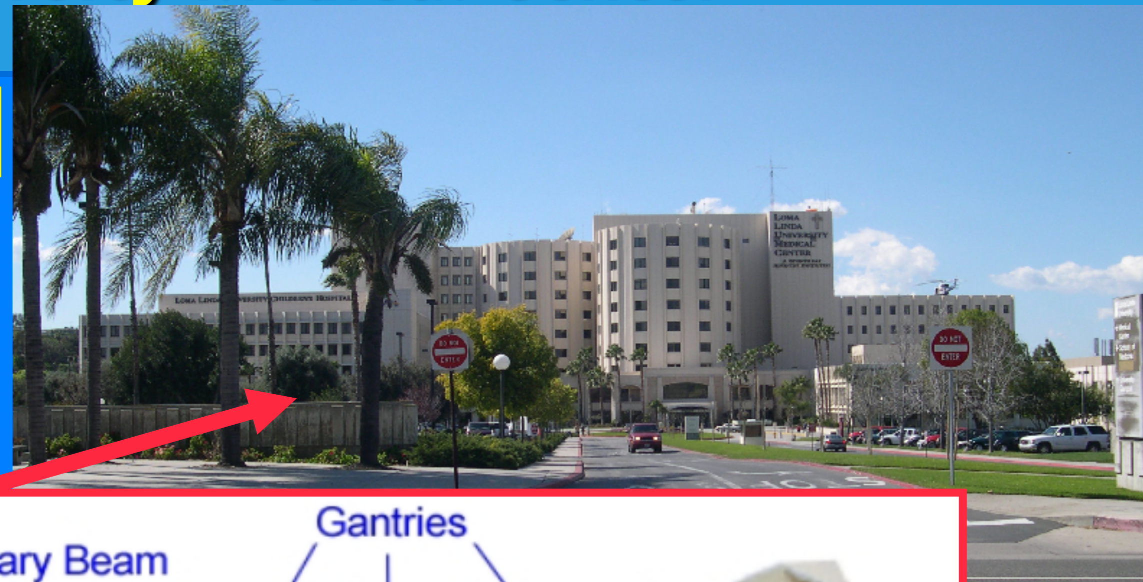
Currently huge momentum in particle therapy

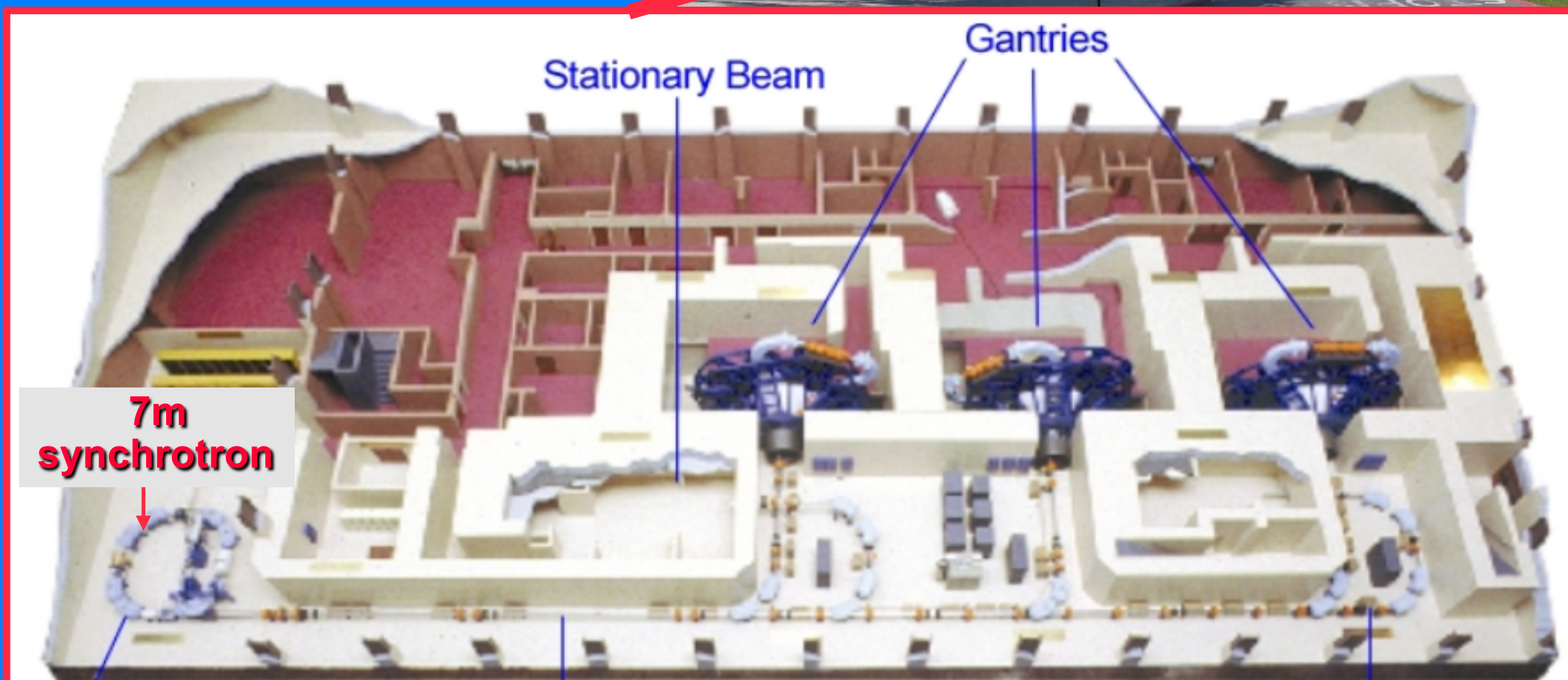




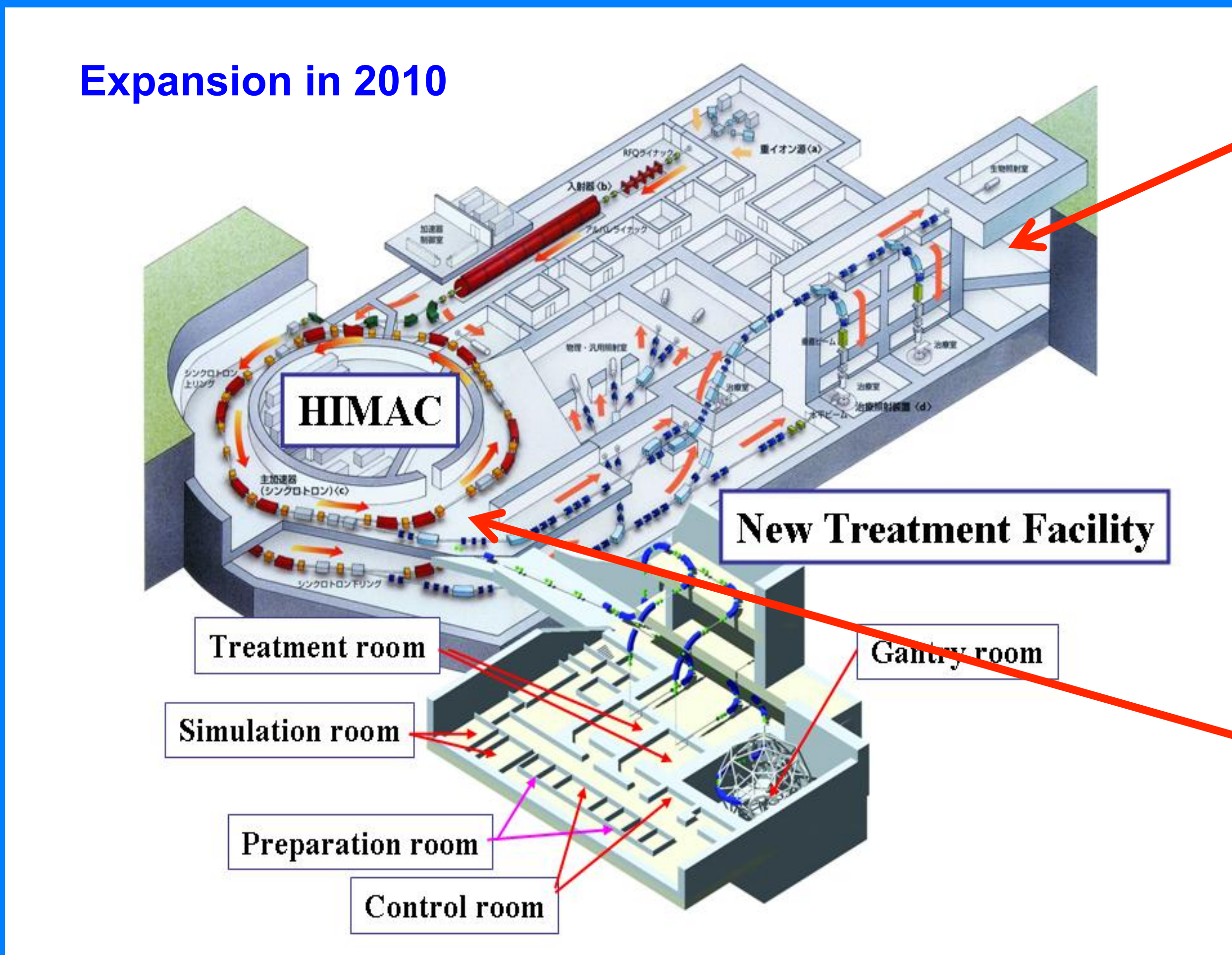
Loma Linda University Medical Center

160 session/day





Carbon Ion facilities: HIMAC (Heavy Ion Medical Accelerator in Chiba)



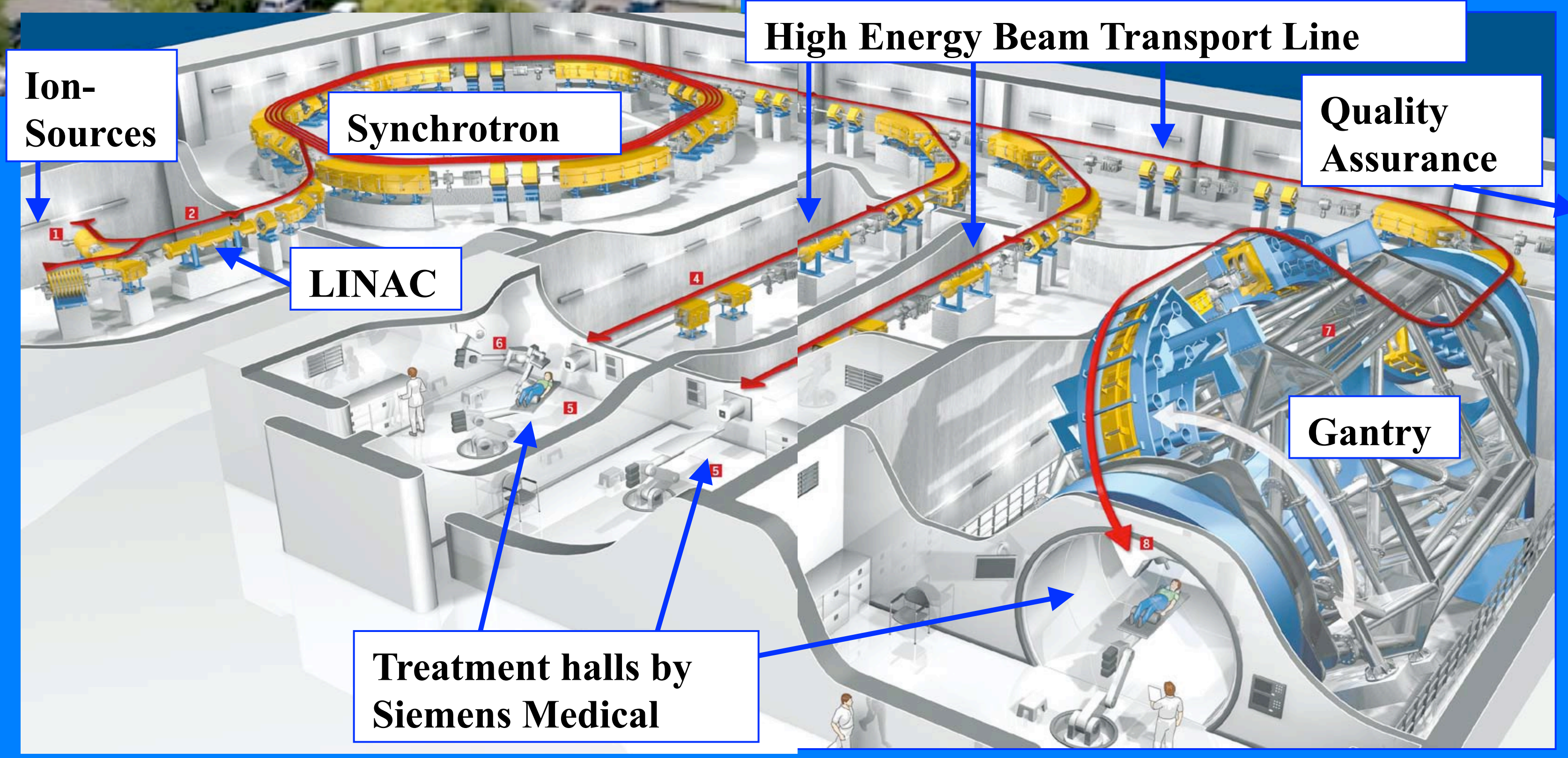
3 treatment rooms
1 experimental room

2 synchrotrons
800 MeV/u,
therapy and
nuclear physics

HIT - Heidelberg

First patient: end 2009

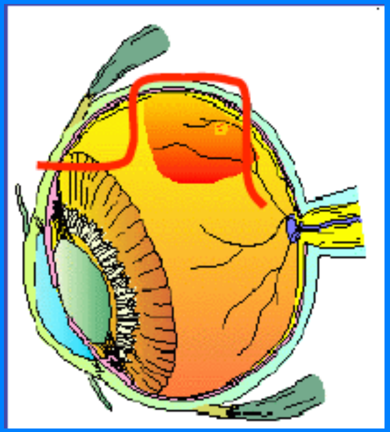
So far >2.700 patients

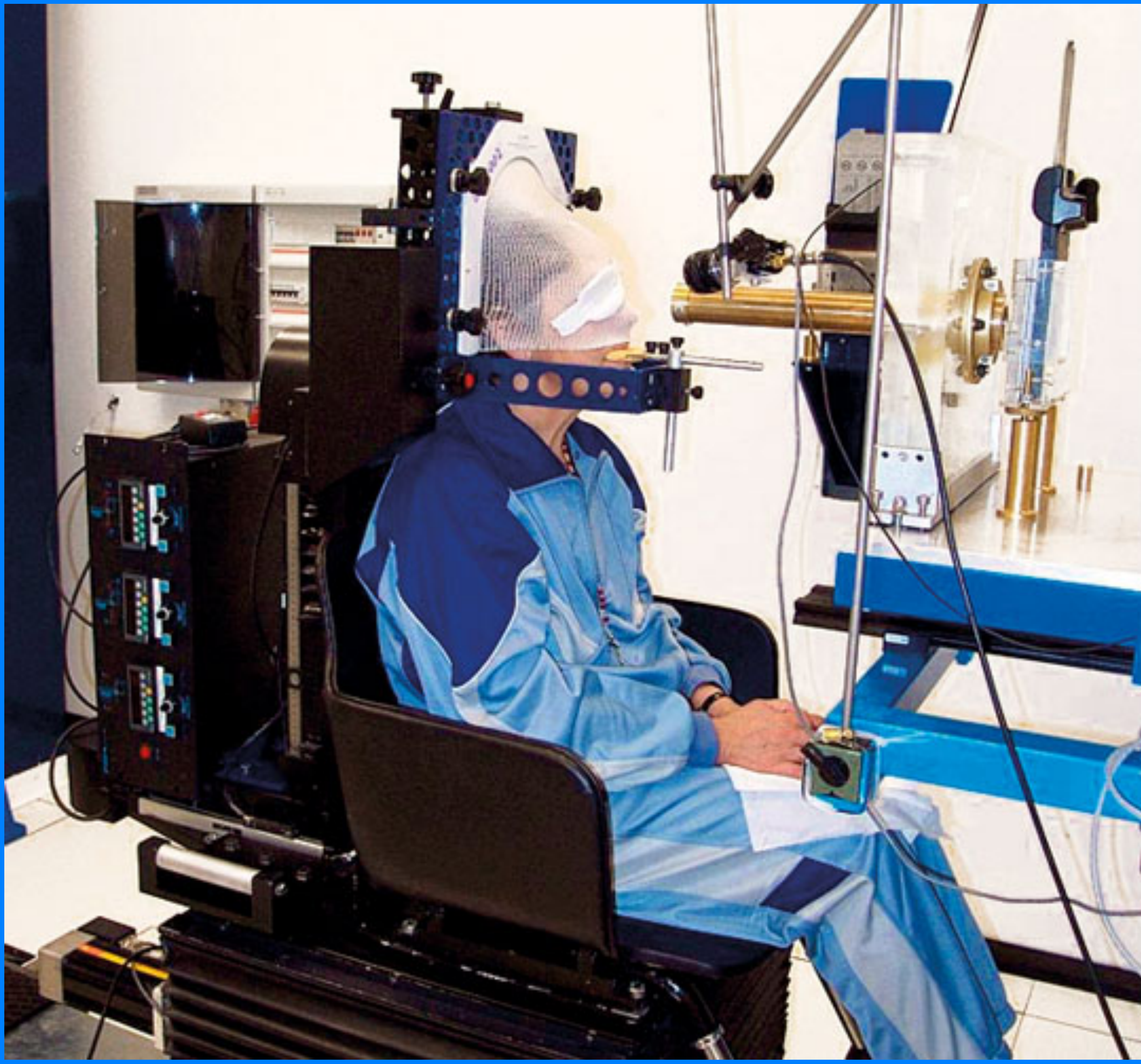


HadronTherapy in Italy

CATANA @INFN-LNS

- **>350 patients since 2002**

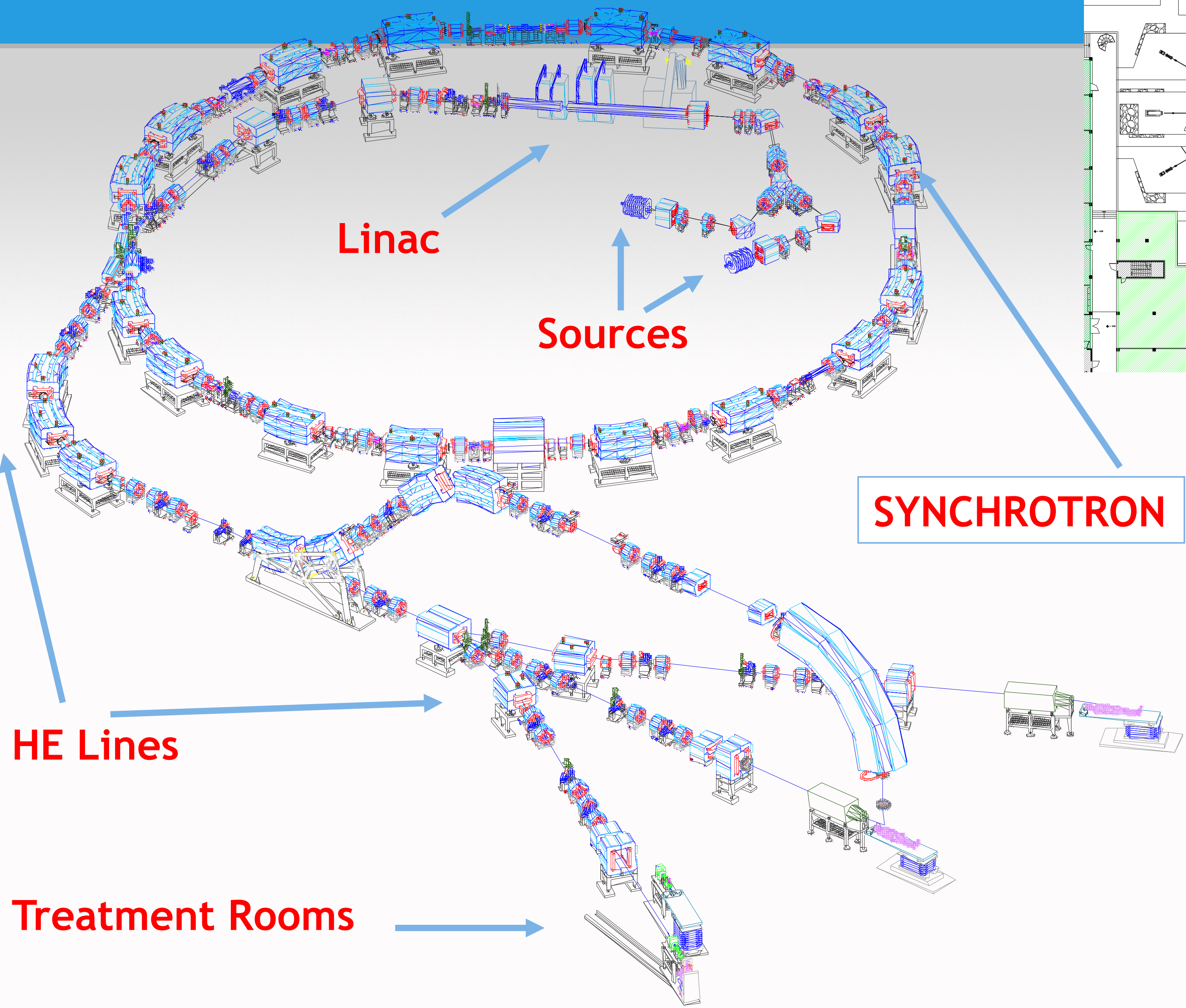


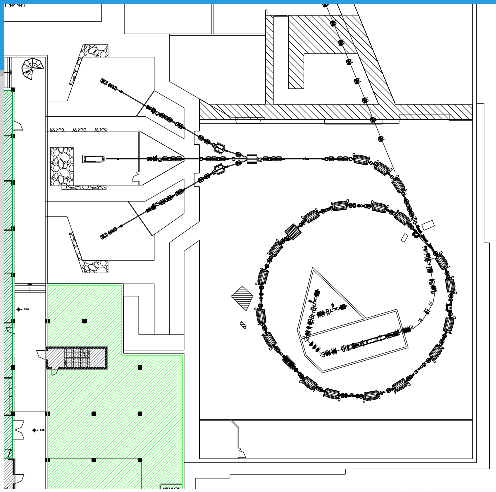


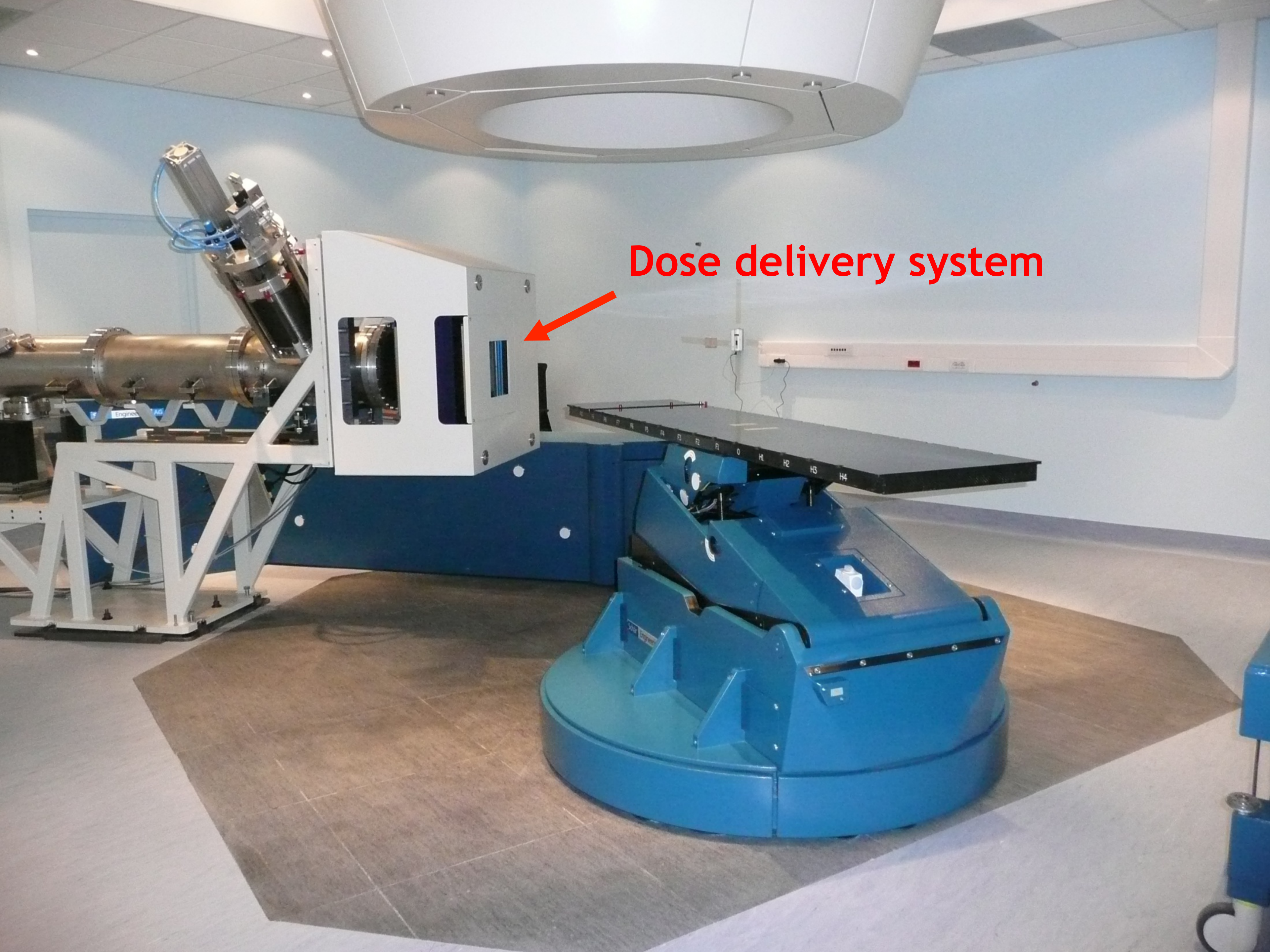
Treatment of thechoroidal and iris melanoma (In Italy about 300 new cases for year)

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

Il sincrotrone del CNAO





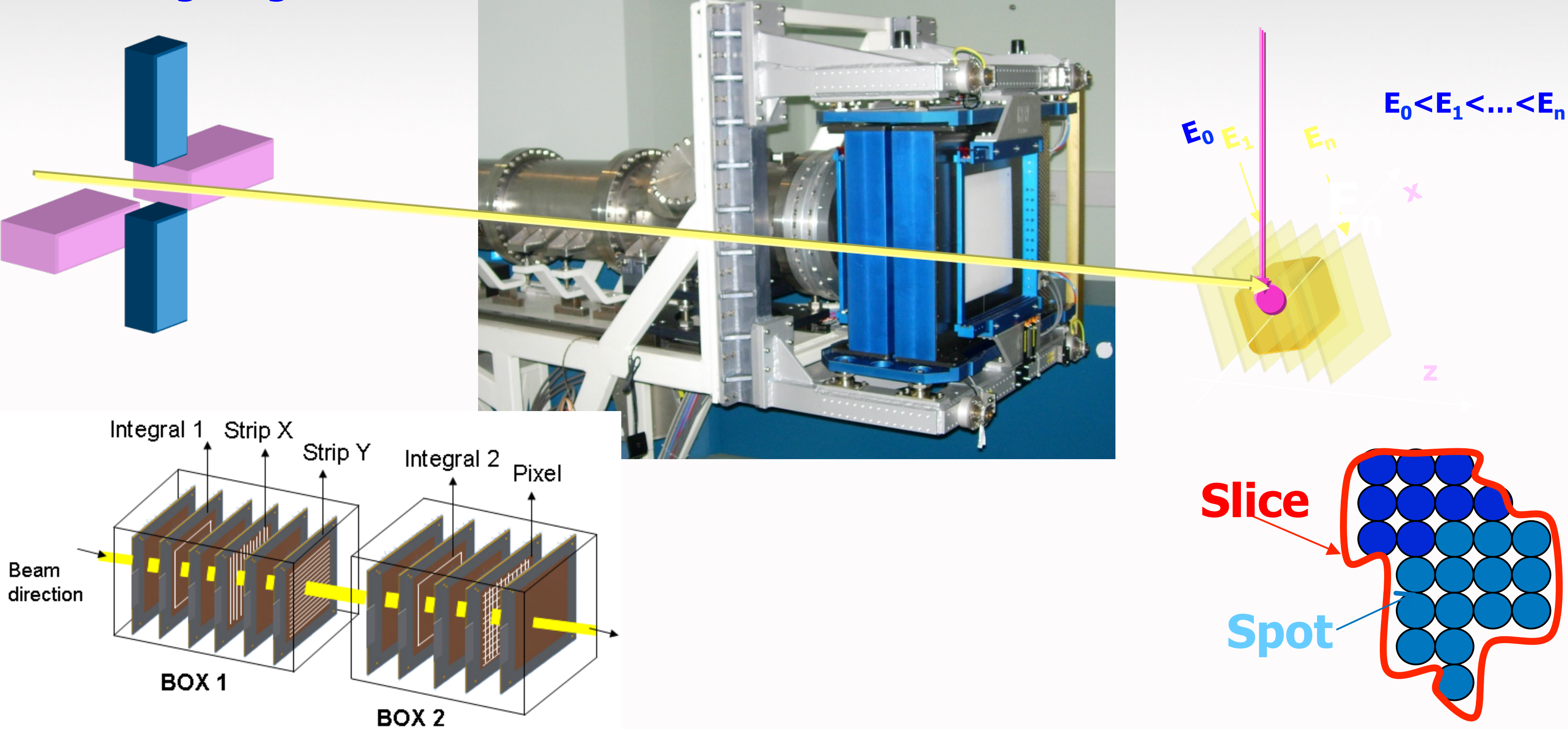

Dose delivery system

Beam/Dose Delivery system in CNAO

Nozzle and monitor system

Scanning magnets

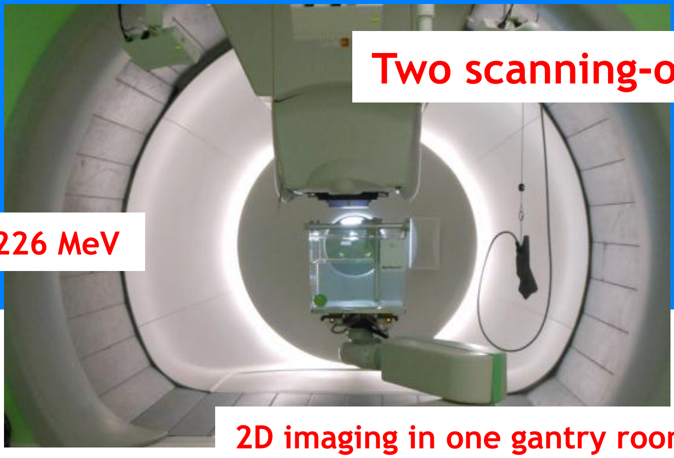
Isocentro



22 September 2011
First treatment session at CNAO (protons)

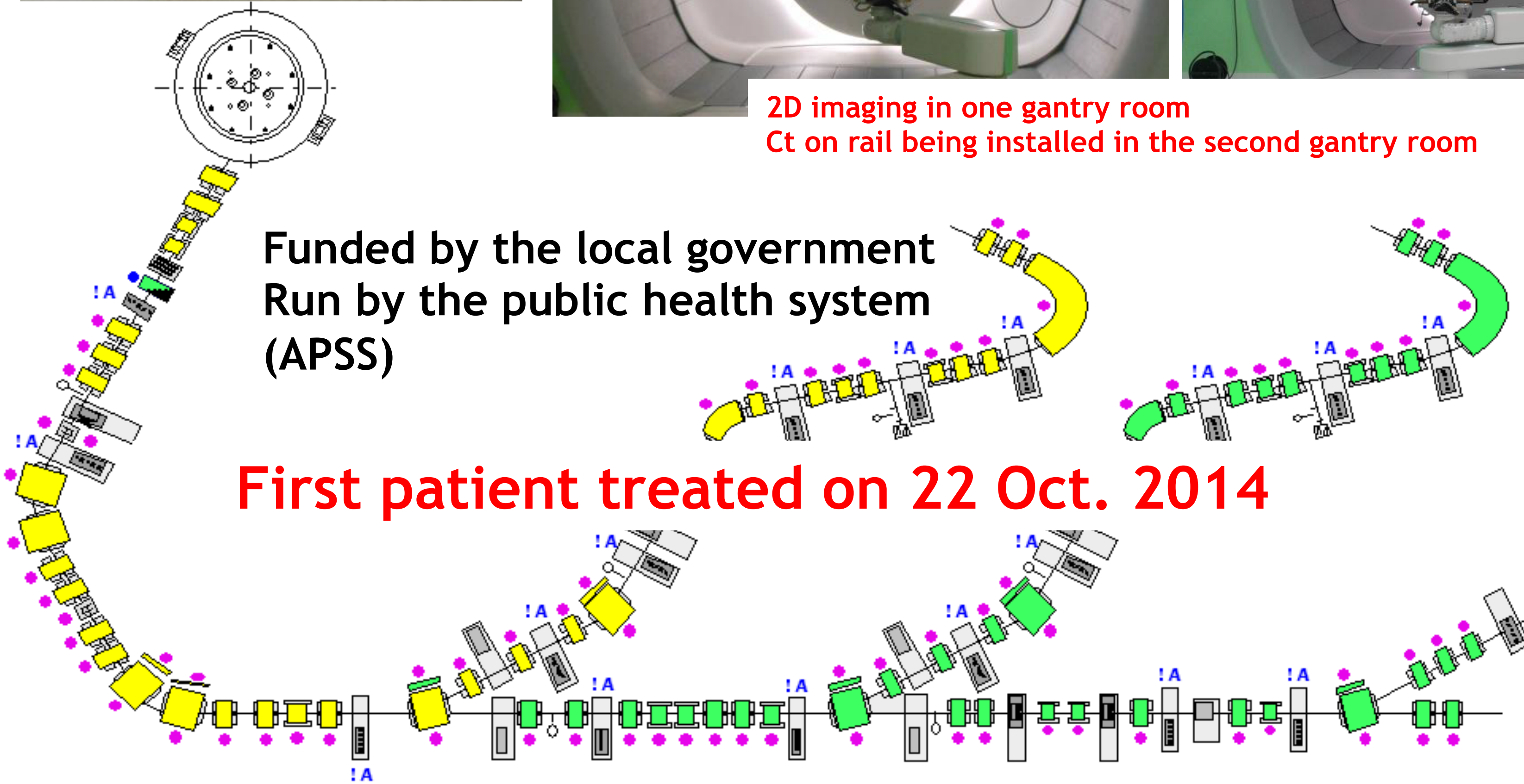
Proton Therapy in Trento (Italy)

Energies at isocentre from 70 to 226 MeV



Two scanning-only 360°gantries

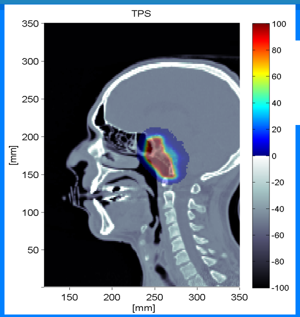
2D imaging in one gantry room
Ct on rail being installed in the second gantry room



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

First patient treated on 22 Oct. 2014

Software: Treatment Planning

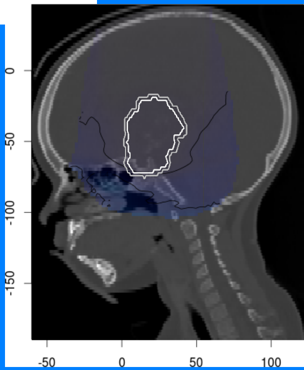


(Effective) Dose Optimization

Imaging:
CT scan
and/or PET-CT)

Electron density

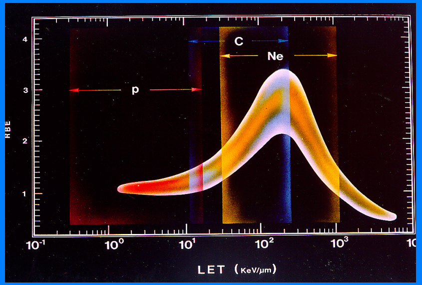
Radiotherapist:
identification of Target Volume and of Organs at Risk

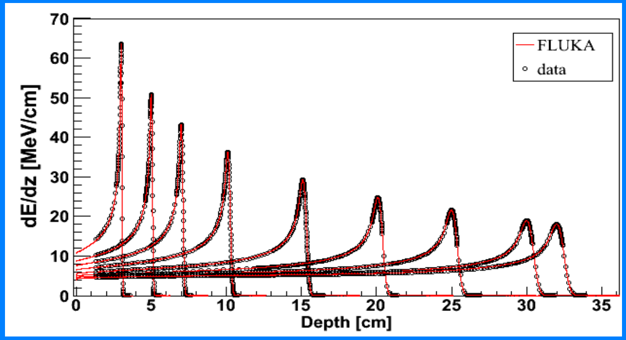


Radiobiology:
RBE parameters
OER (not yet…)

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

Treatment Planning System

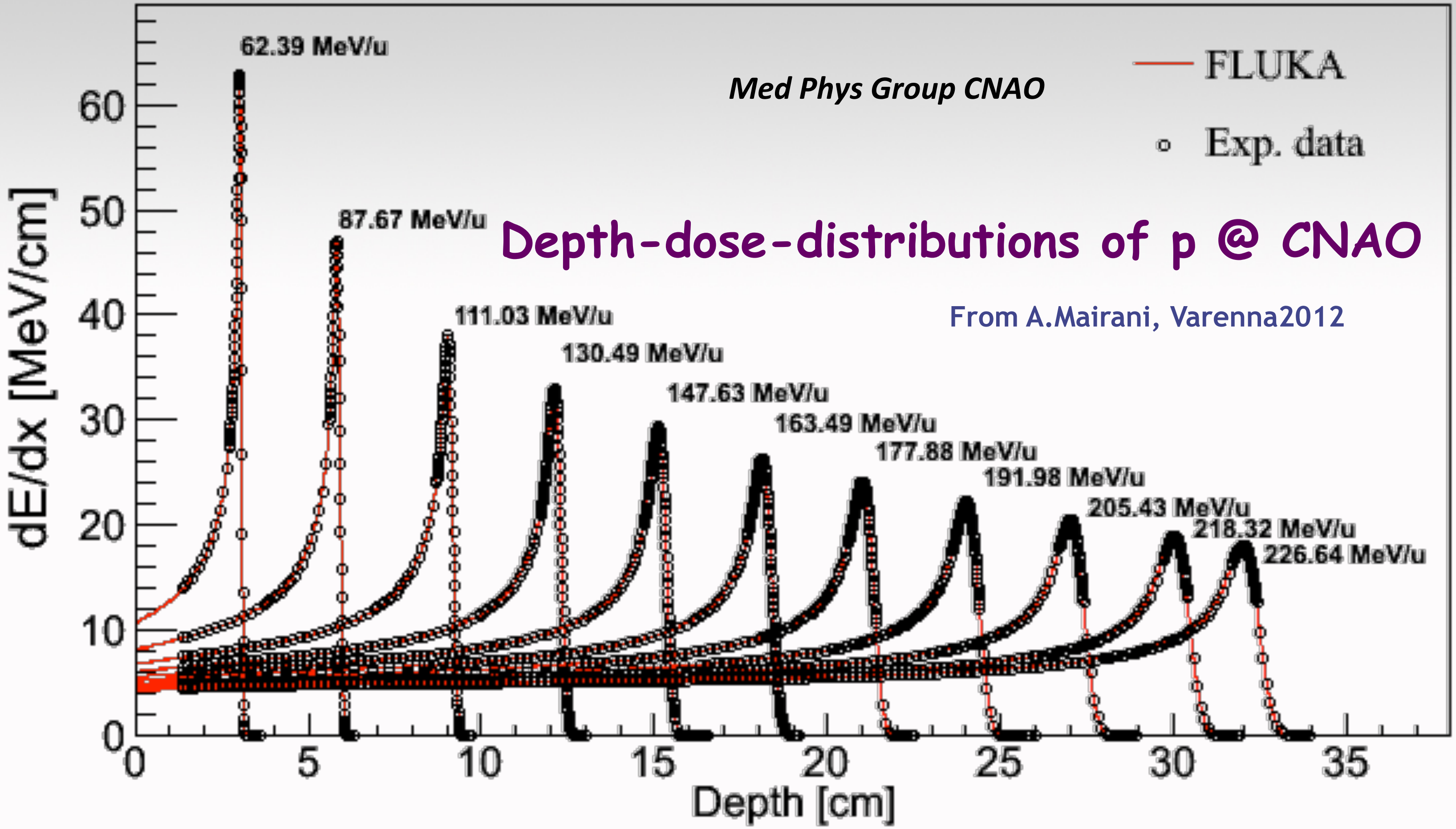




Intensity, position and energies to be delivered to patient

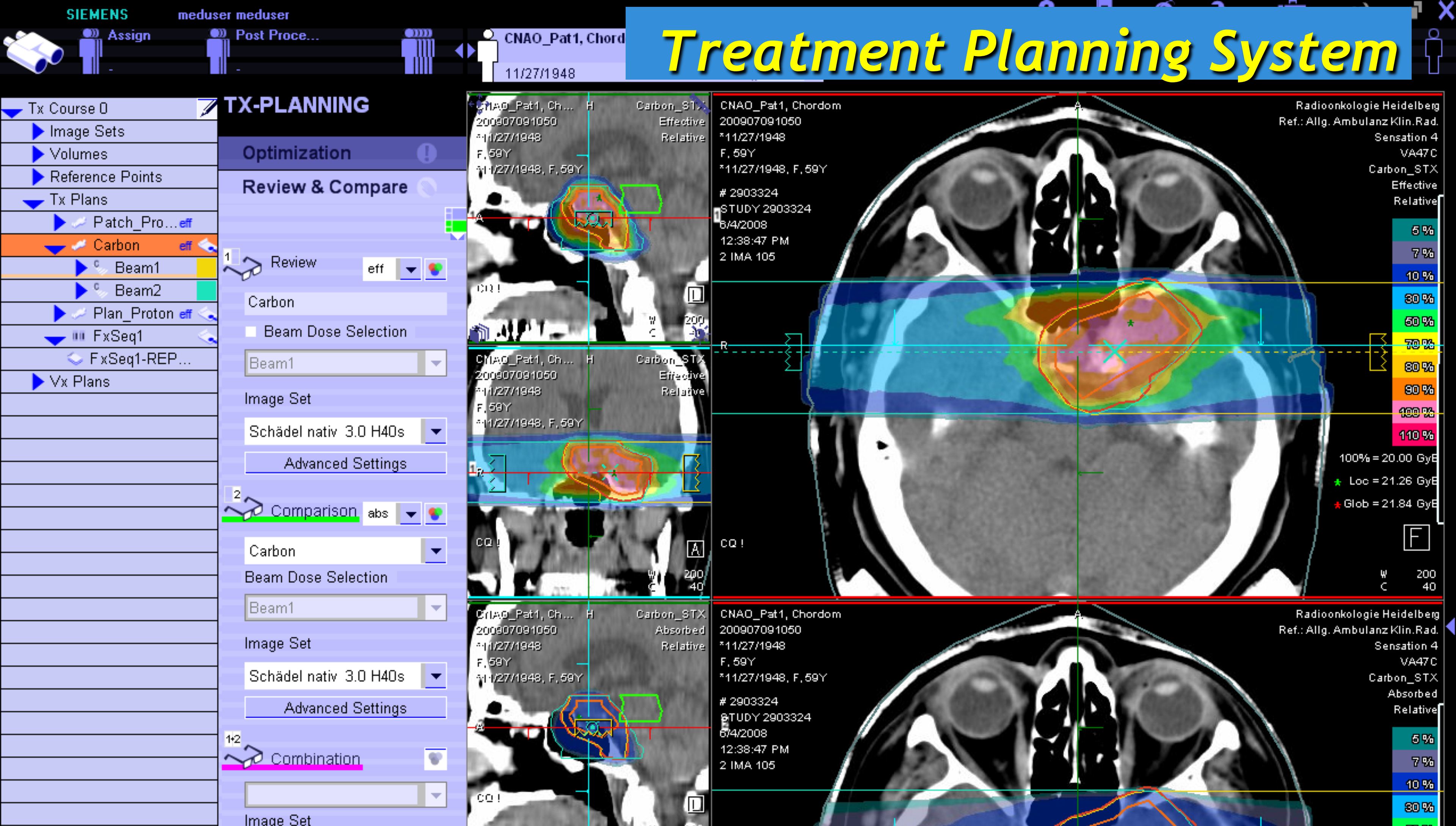
Generation of TPS databases: HIT, CNAO, …

Used for generating p, ^{12}C dose vs depth databases then used for TP



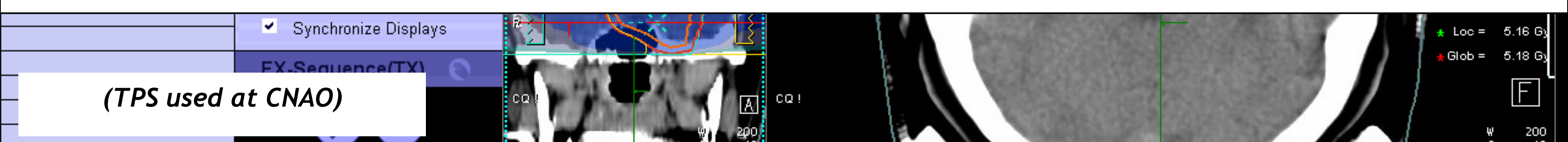
Experimental verification in water wo/with RiFi for the 147 energies in the initial phase of the operation

Treatment Planning System



TPS is directly related to scanning modality and RBE evaluation model

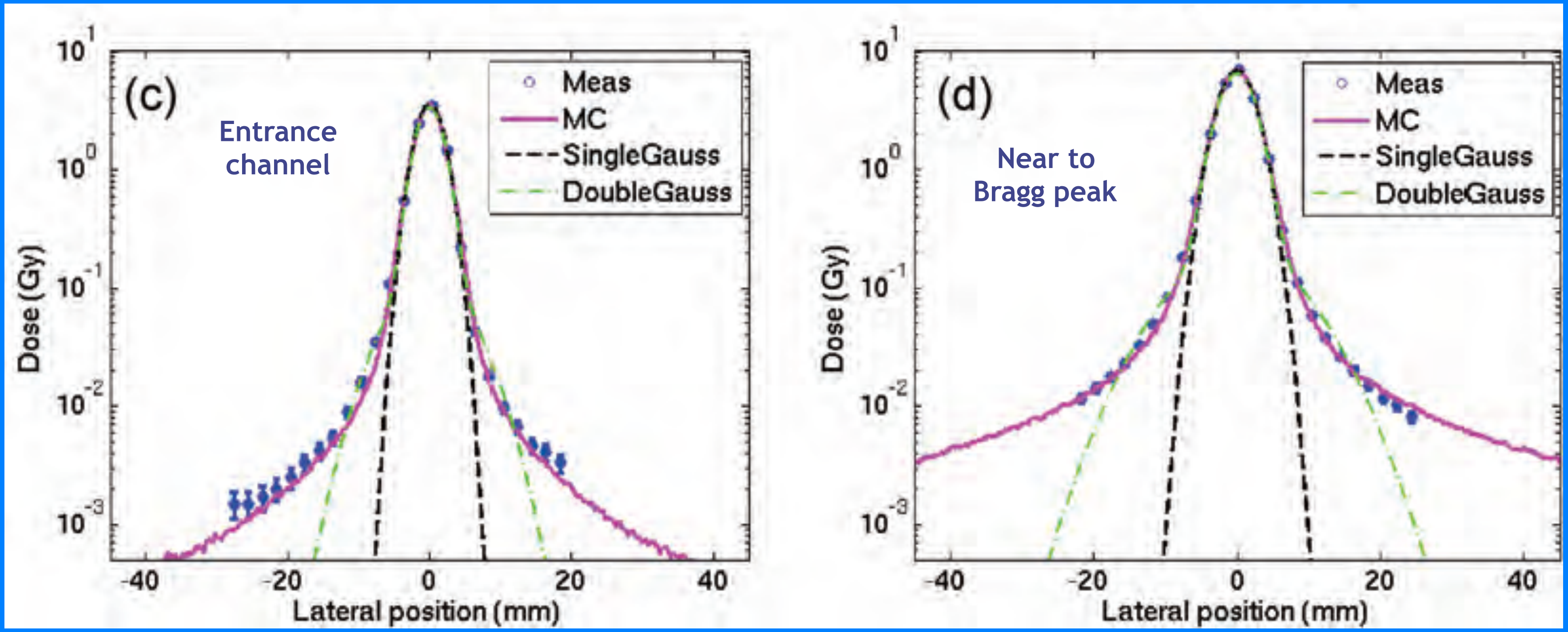
Need to include management of moving organs and integration of in-room imaging



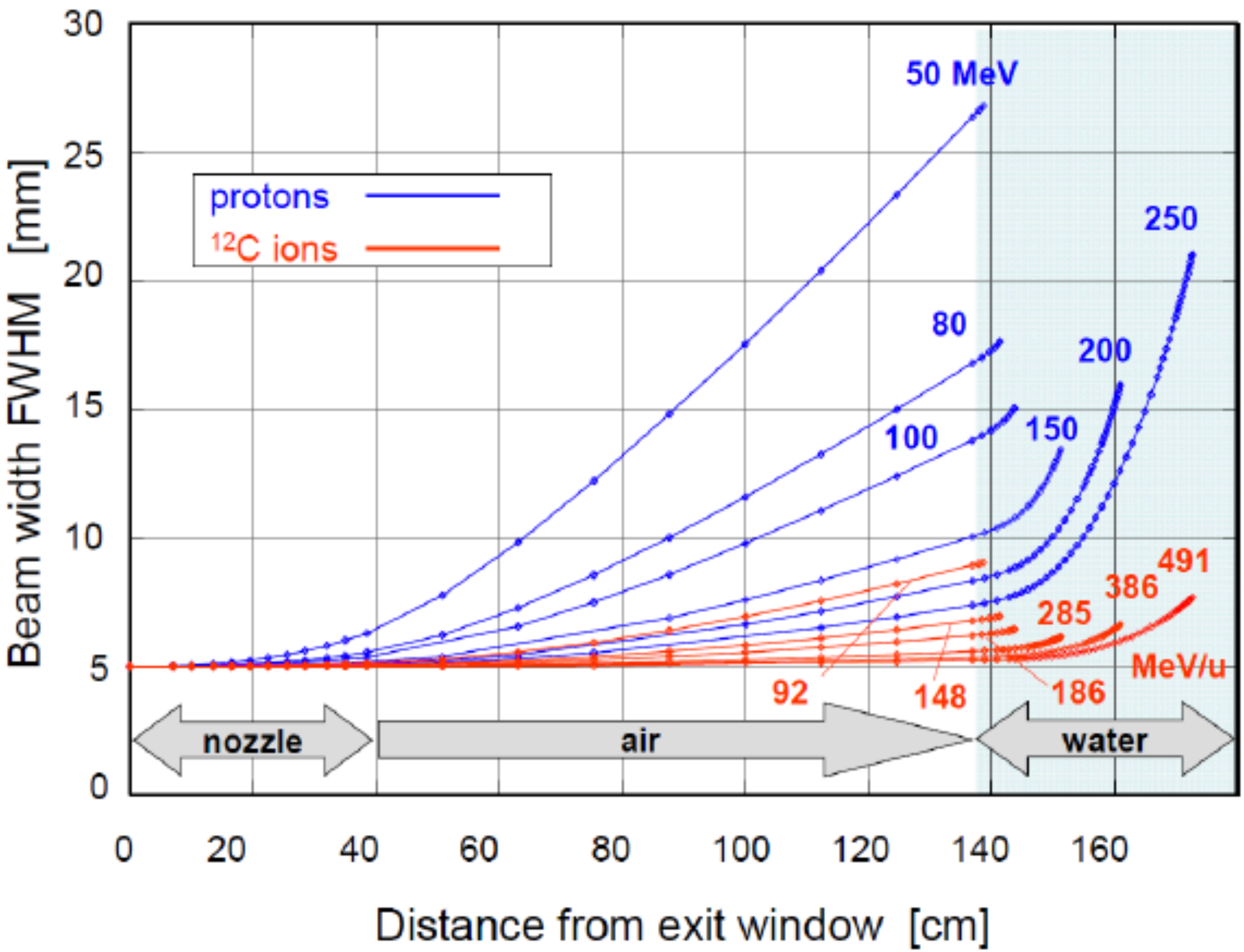
(TPS used at CNAO)

Ion Therapy: the lateral scattering

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

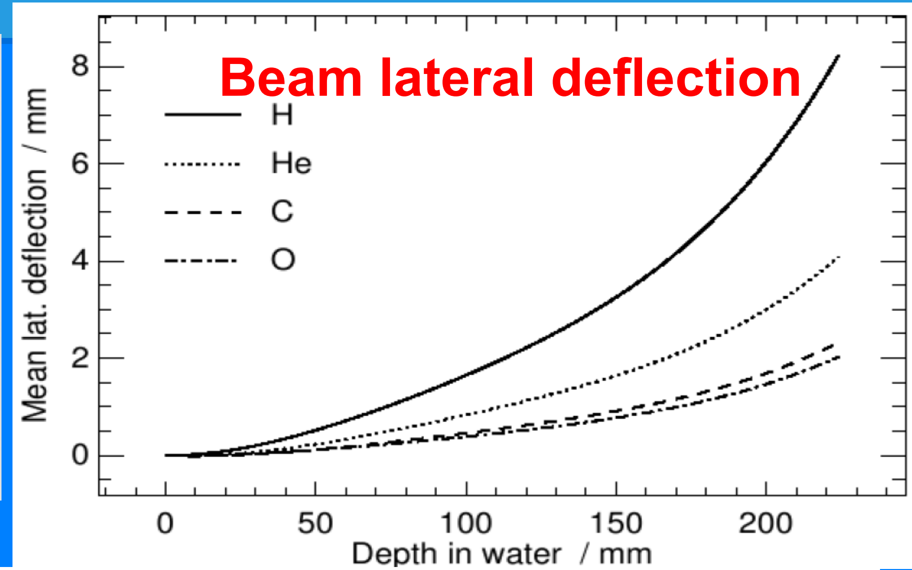


Measured lateral distributions with corresponding MC simulations (normalized to the data) for carbon ion 299.94 MeV/u beams in water, sampled at a depth of ~1.5 cm in the entrance channel (left, c) and of ~16.5 cm shortly before the Bragg peak (right, d). The double Gauss fit of the experimental data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



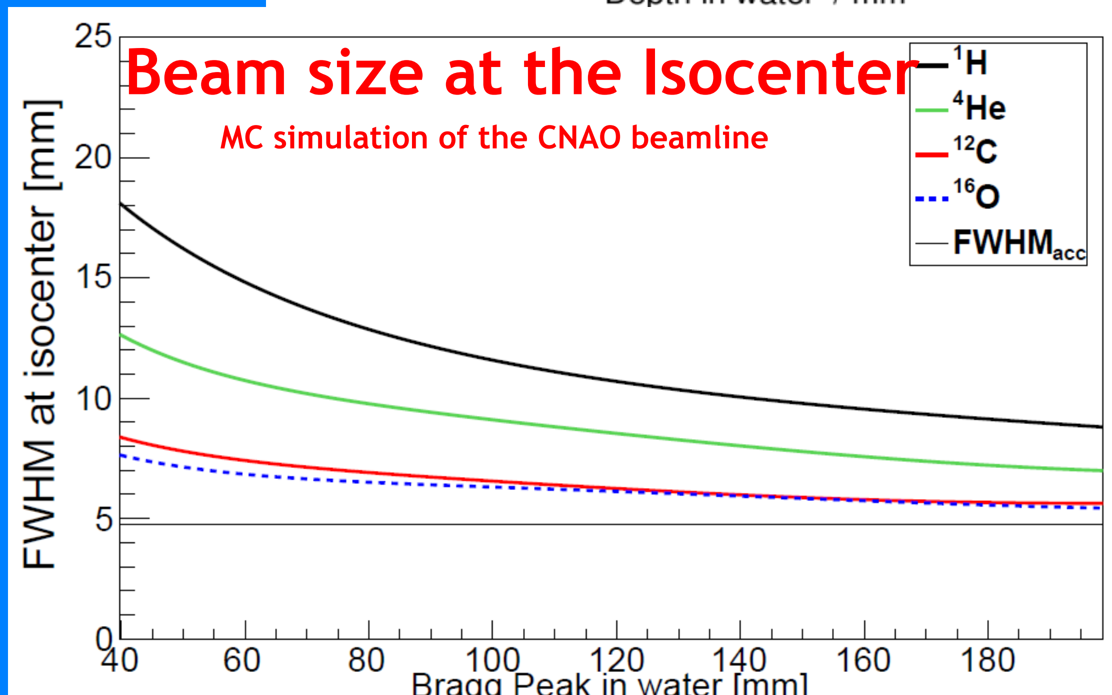
protons
12C ions
50 MeV
80
100
150
200
250
92
148
186
285
386
491
MeV/u
nozzle
air
water
Beam width FWHM [mm]
Distance from exit window [cm]
0
5
10
15
20
25
30
0
20
40
60
80
100
120
140
160

New ion beams proposed for therapy

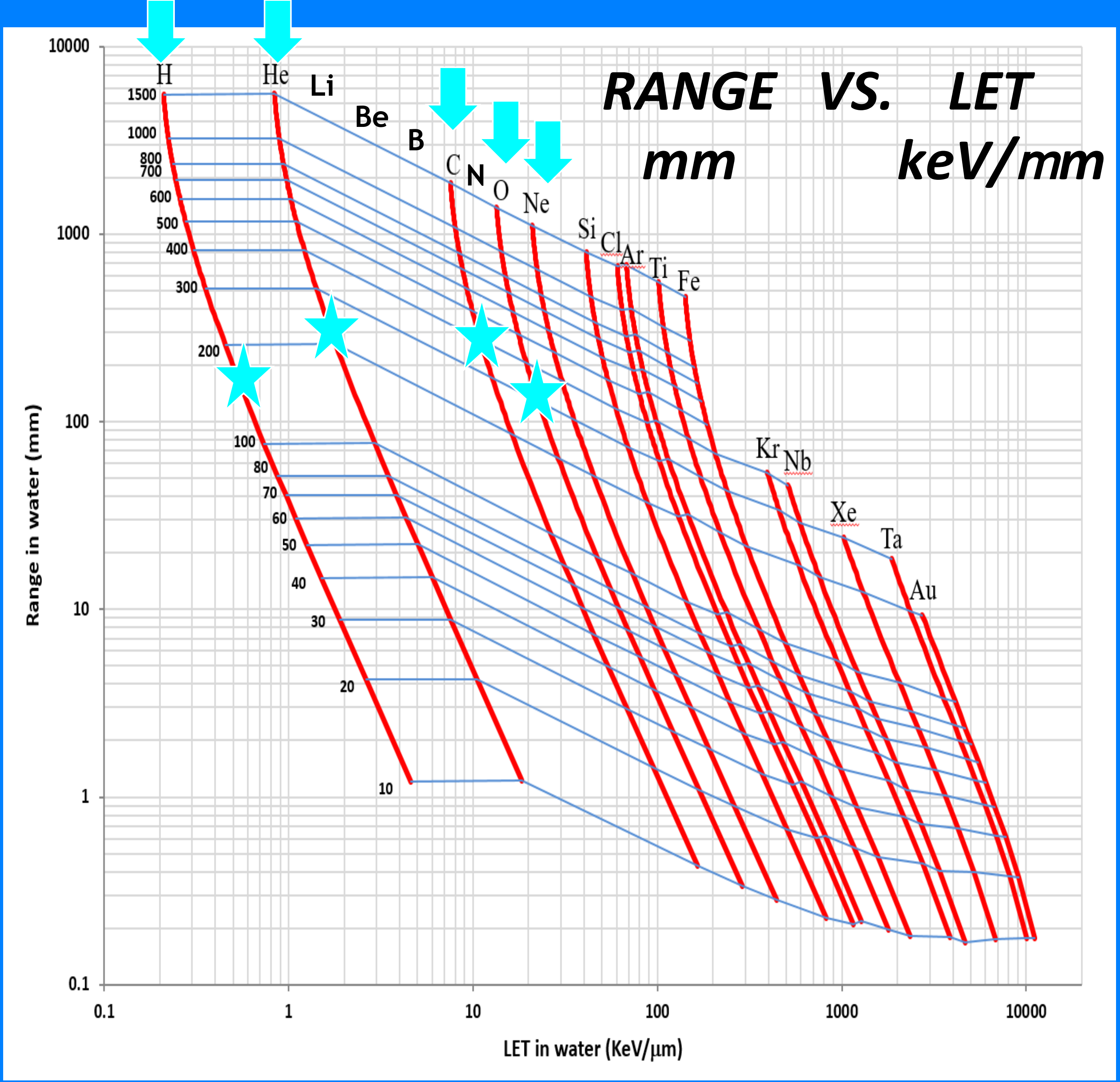


^{4}He (50-300 MeV/u):
negligible fragmentation, higher RBE than protons, but more limited lateral scattering

^{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



NSRL BEAMS
Brookhaven
National
Laboratory

Adam Rusek
2015

The contribue of physics to particle therapy development

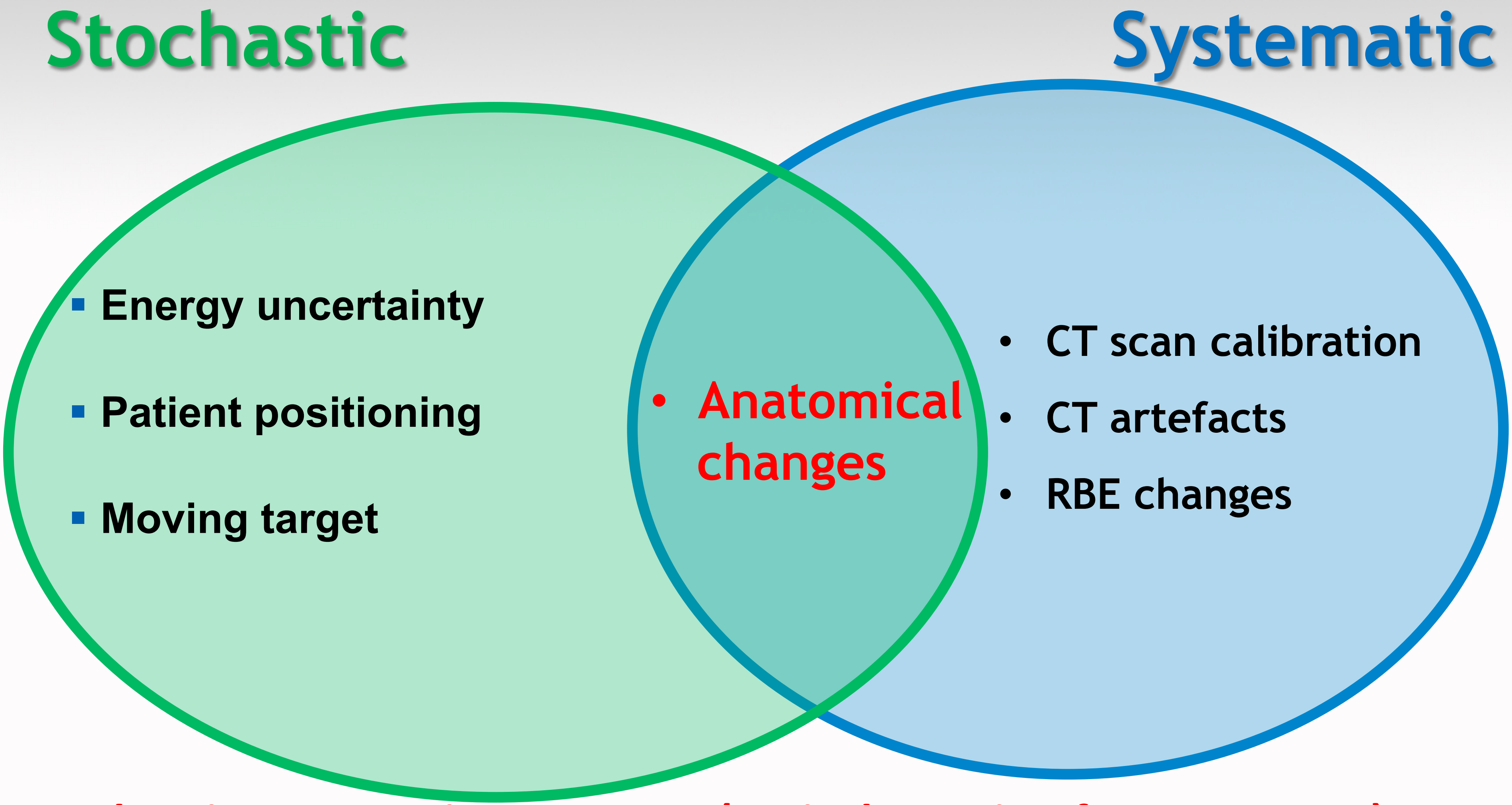
There is still a significant fraction of people in the clinical community who consider hadrontherapy (ion therapy) too complicate, too expensive, not able to reach in practice the expected high level of precision, not yet in the realm of evidence-based medicine

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 remains fundamental

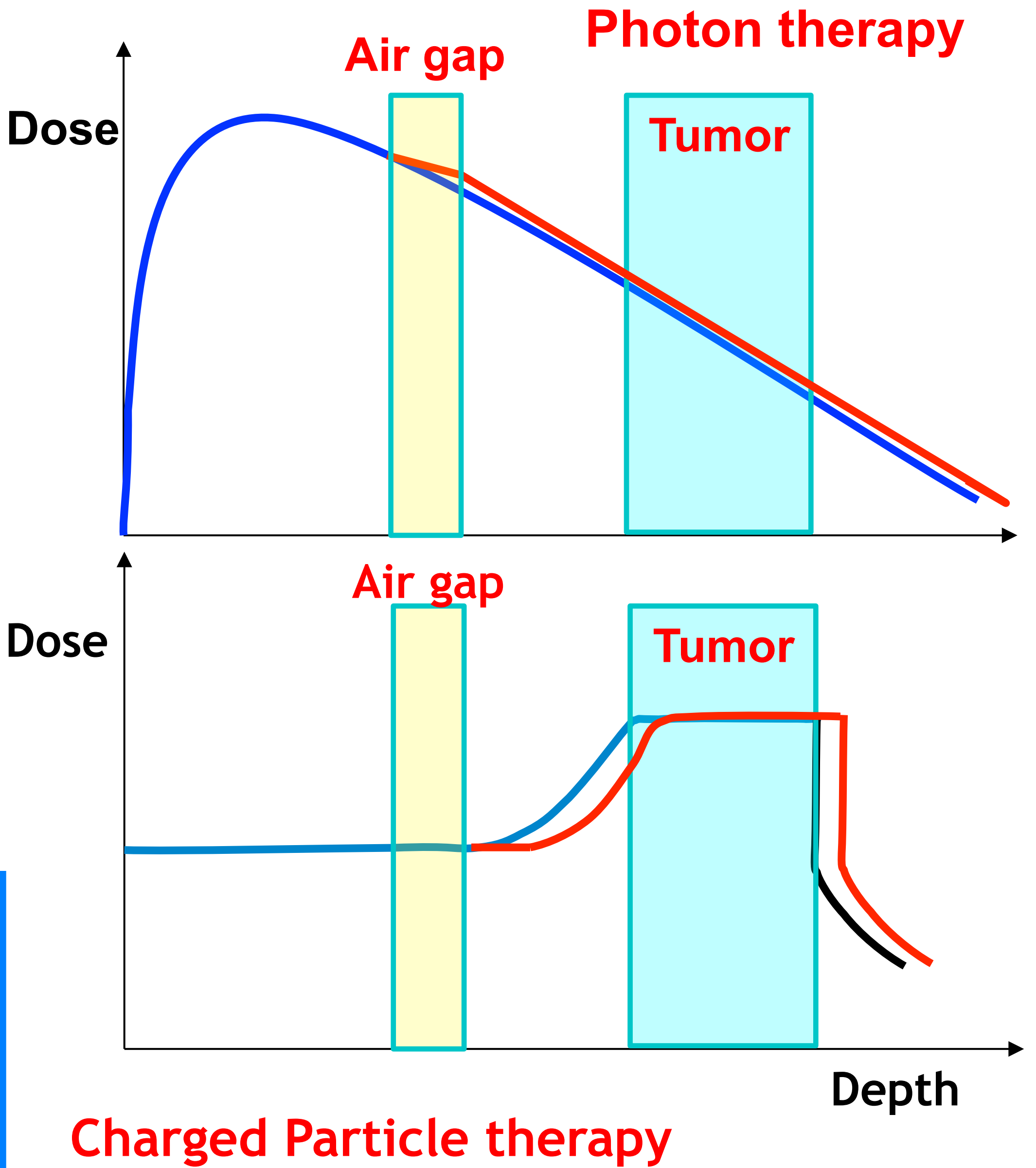
A case for research: Range Uncertainties



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

Range Uncertainties and Anatomical Changes

- 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

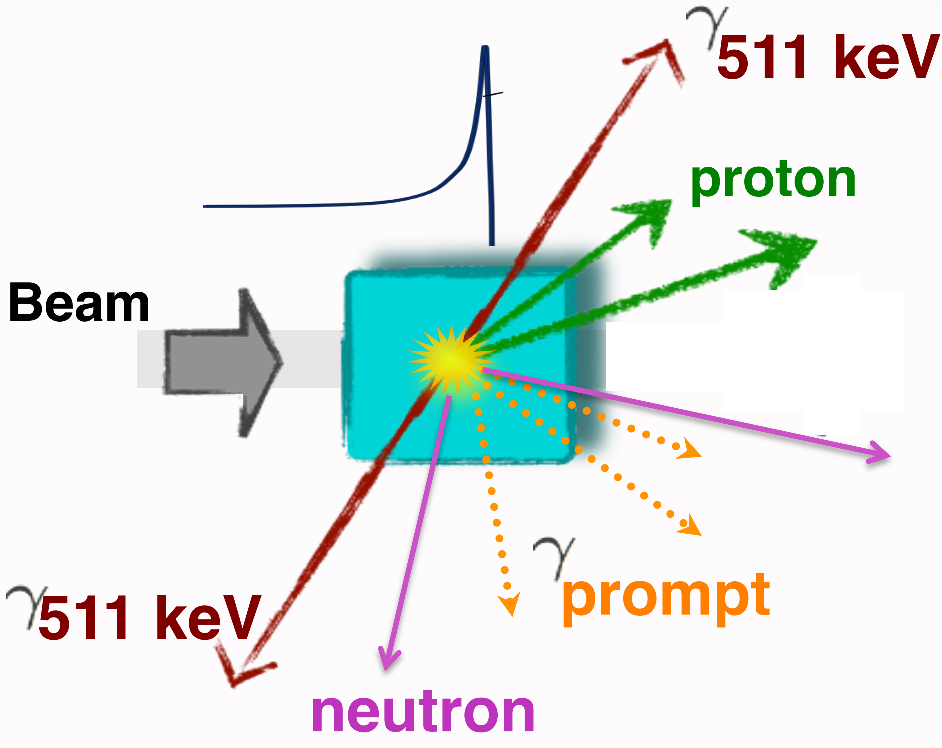


Help from Nuclear Physics: exploiting secondary products

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

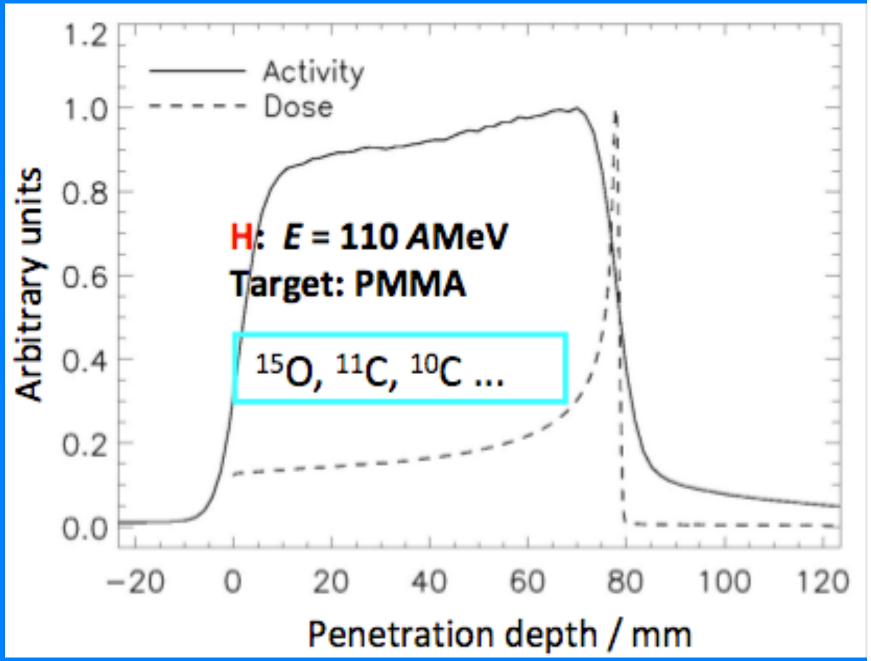
- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) with respect to conventional PET (hours)
- Low activity asks for quite a long acquisition time (some minutes at minimum) with difficult in-beam feedback
- Metabolic wash-out, the β^+ emitters are blurred by the patient metabolism



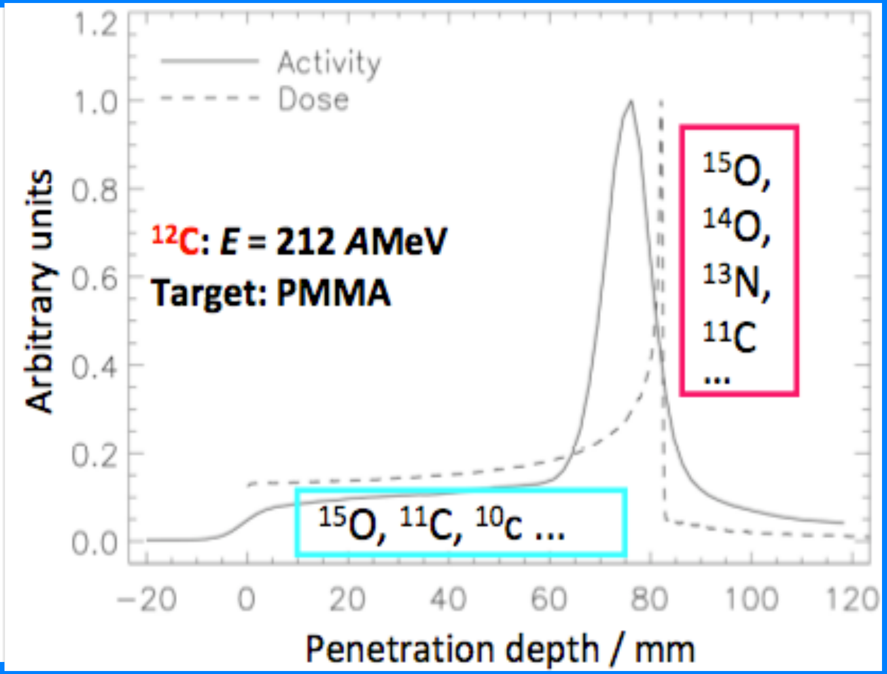
Main example: correlation between β⁺ activity and dose profile

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

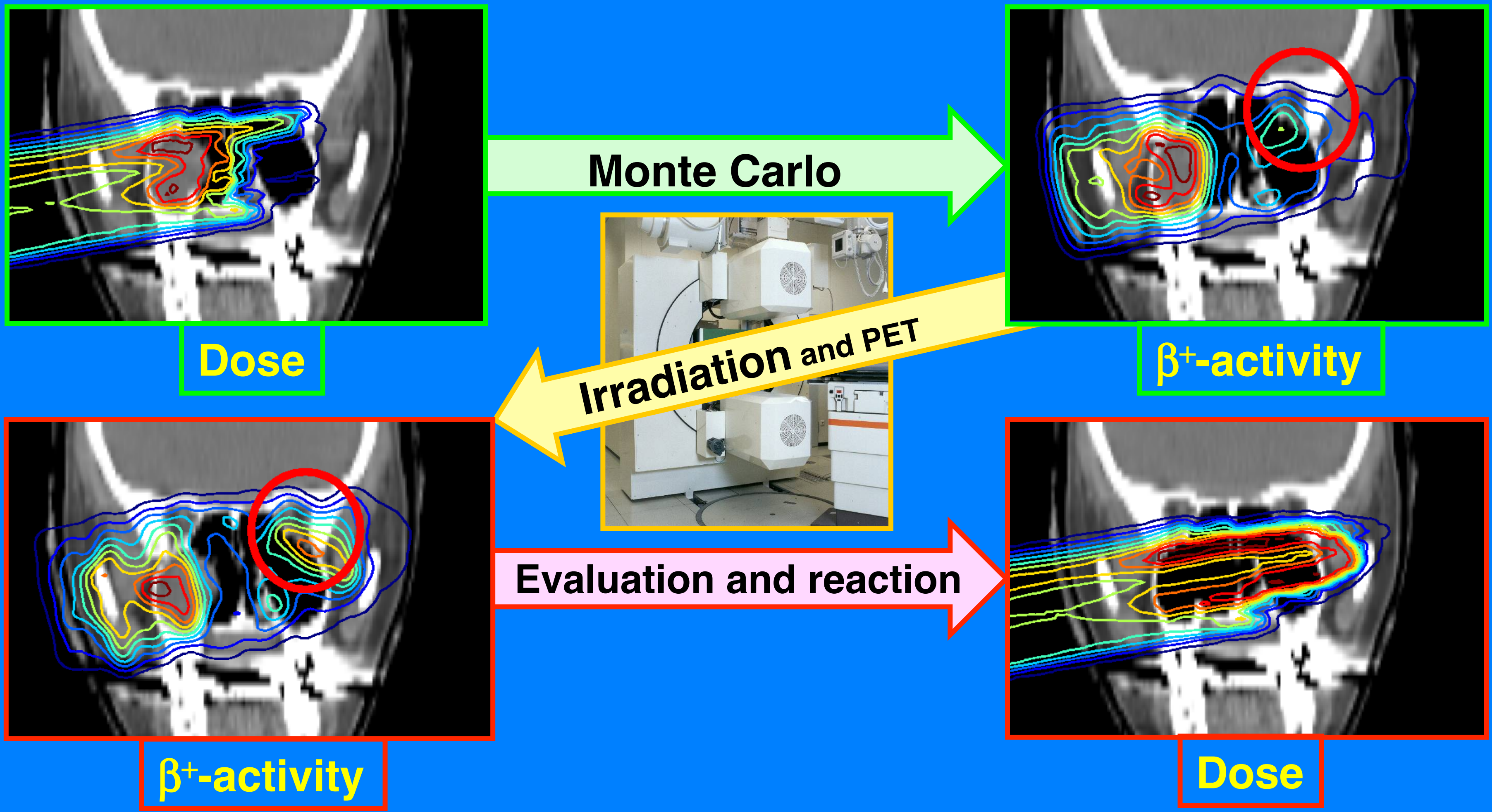


Projectiles & target fragmentation



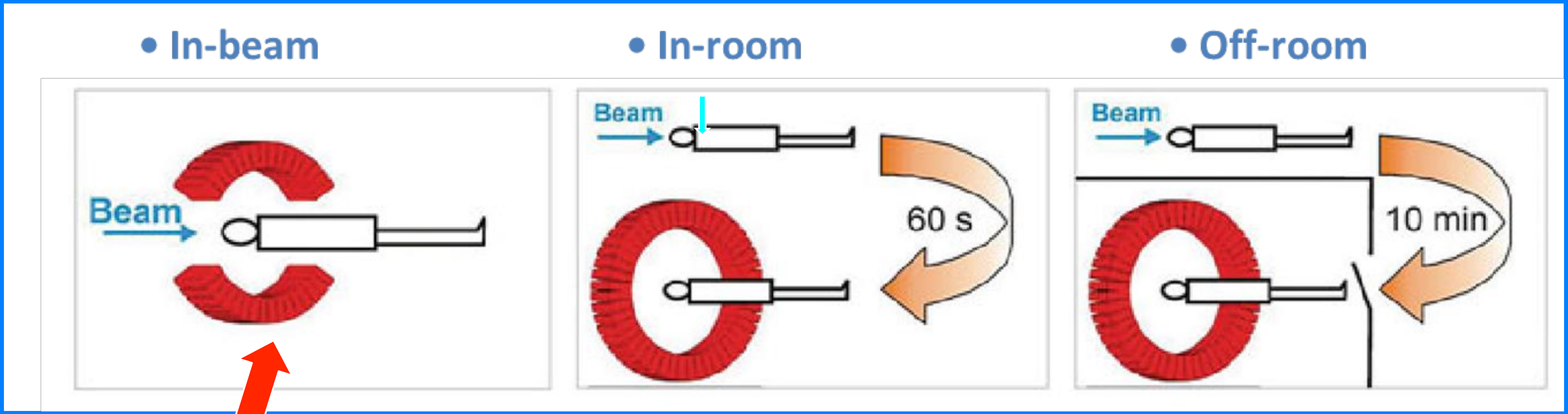
In-Vivo range measurement with PET: workflow and potential

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



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)

Towards real in-beam measurement



Ambition

practice
@Heidelberg

Monte Carlo codes: the need for exp. data

MC are becoming more and more fundamental for:

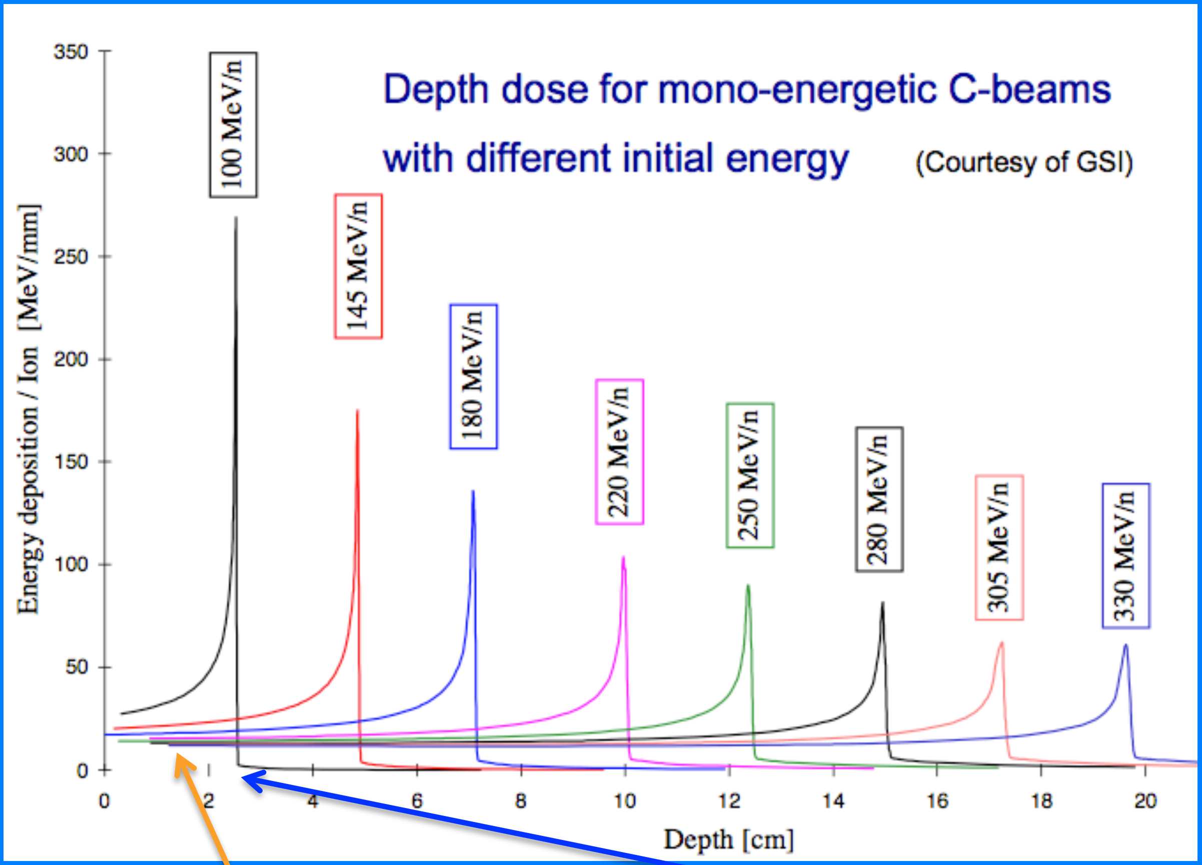
- startup and commissioning of new facilities and beam line stuides
- database generation for Treatment Planning System commissioning
- Treatment Planning verification (and correction)
- Prediction and analysis of secondary production by hadron beams for monitoring purposes
- Study of detector response

Main important features

- Physics
- Overcoming Water Equivalent Path Length 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…

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



LNS 62AMev C beam (2009)

GANIL 95AMev C beam - E600 collaboration (2011)

GANIL 50AMev C beam

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…)

What clinicians ask today to Particle Therapy

- High quality clinical data for high level evidence
- Health economic assessments; global epidemiological assessments
- Improved clinical research structures, including IT
- Radiobiological core data (e.g. RBE)
- Integration into precision medicine era (e.g. biomarkers, combined modality effects)
- Range uncertainty reduced
- Control of organ motion, of anatomic changes during treatment, of biological changes during treatment
- Full image guided adaptive RT equipment
- Lower cost

M. Baumann

OncoRay

Taking full advantage of particle therapy in terms of physics requires:

✓ Full image guidance (real time)
✓ Reduced range uncertainties (real time beam imaging)
✓ In vivo dosimetry
✓ Highest level treatment planning
✓ Adaptive algorithms including all items above
✓ Very rapid and exact dose delivery (repainting, tracking)
✓ Reliable simulation tools (and fast !!)
✓ …

Hardware + Software

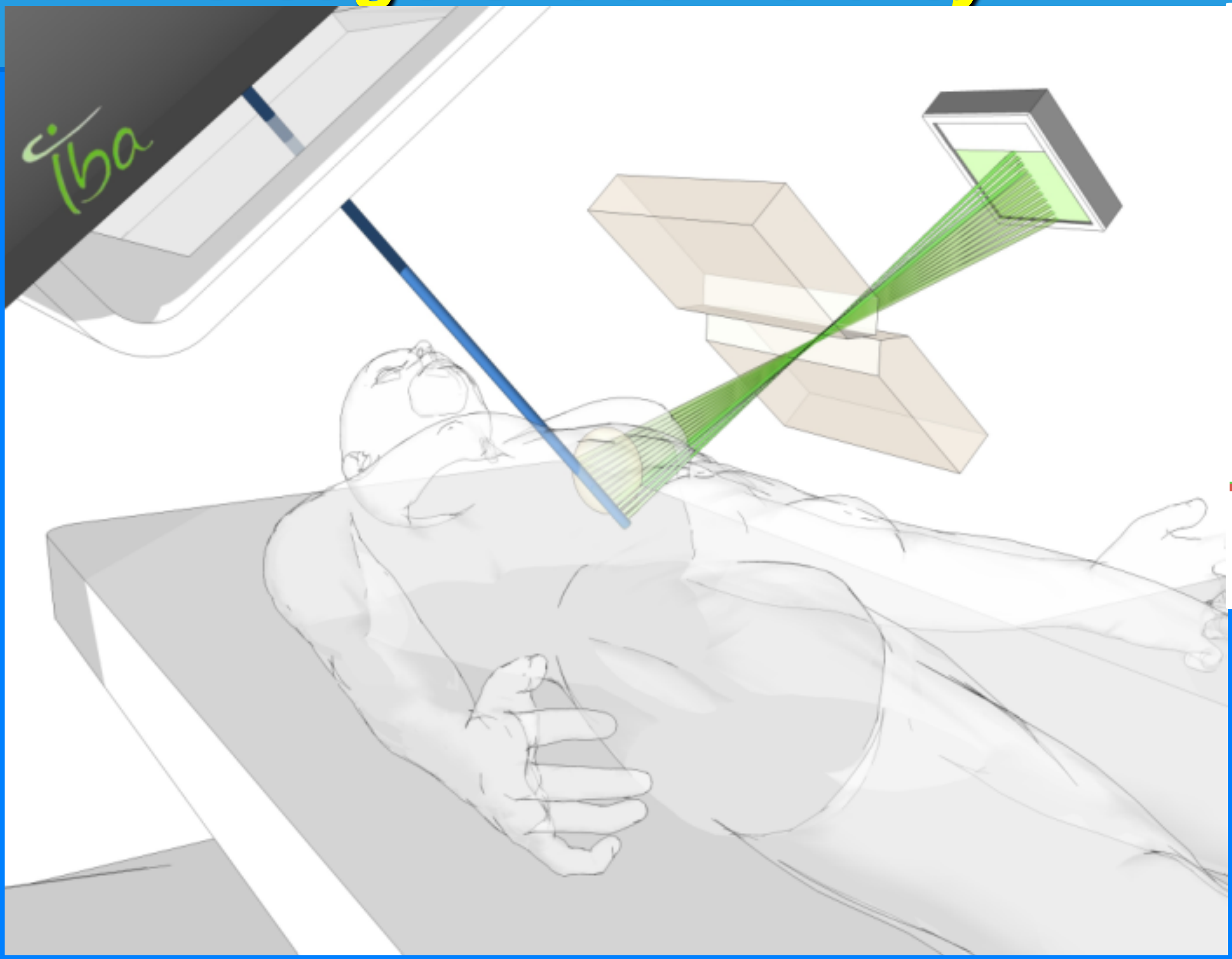
Some research issues to be addressed with the help of Physicists

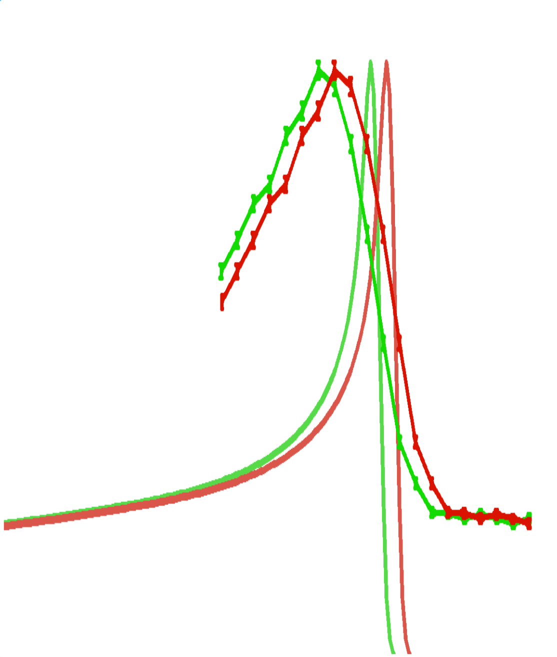
- Biologically oriented Treatment Planning
- Fast MC (including MC treatment planning)
- Ultrafast treatments -> Higher intensity beams
- Treatment of moving organs
- Hypofractionation, Radiosurgery (single fractions for cancer and non-cancer diseases) ⇒ Range check mandatory
- Image-guided hadrontherapy
- Fully assesed Range Monitoring techniques
- Dose verification methods
- Accelerator developments and cost reduction
  - New components
  - Compact acceleration systems
  - Future: new acceleration techniques towards more compact structures ⇒ Laser driven Plasma acceleration ?

Thank you for the attention

Acknowledgmentes:
V. Patera (INFN, UniRm1,Centro Fermi),
A. Mairani, M. Pullia, S. Rossi (CNAO), M. Schwarz (APSS, Trento),
I. Mattei, S. Valle (INFN-Mi), S. Muraro (INFN-Pi)

Knife-edge-slit camera by IBA

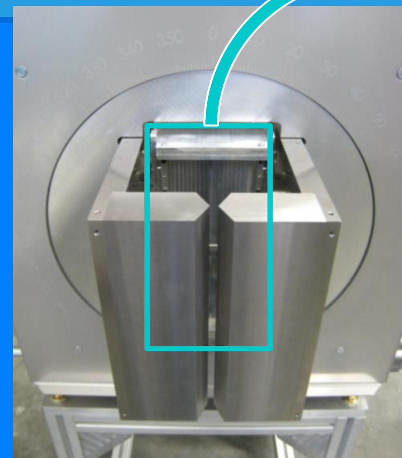




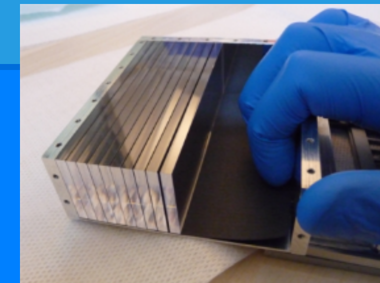
Collimator, software and project PI

The Gamma camera: detector and electronics

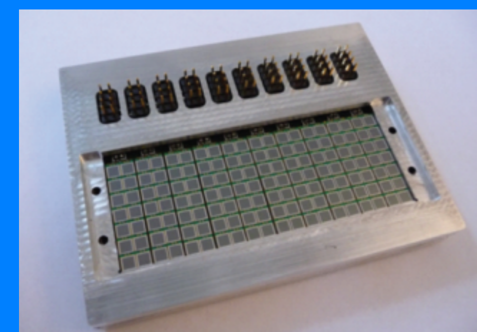
Detector and Electronics



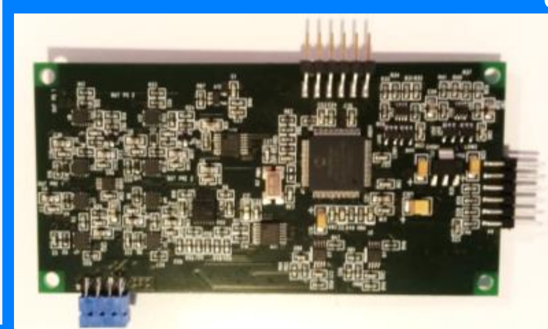
53 kg W collimator for a 10 cm FOV



500 cm³ LYSO distributed in 2 rows of 20 slabs

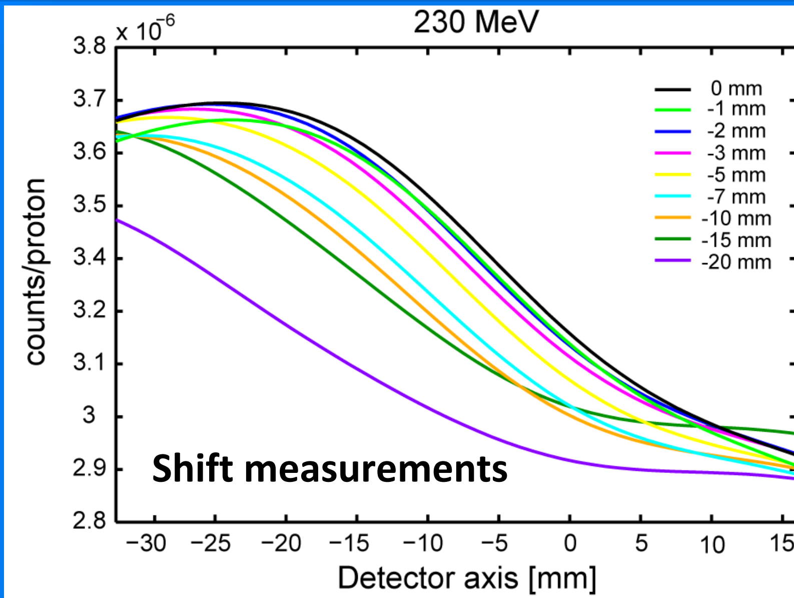


Light readout of one extremity of each LYSO slab by a row of 7 SiPM



40 independent acquisition channels operating in two modes (slow calibration and fast counting)

Experimental Validation



Clinical partner

OncoRay
TECHNISCHE UNIVERSITÄT DRESDEN
HZDR

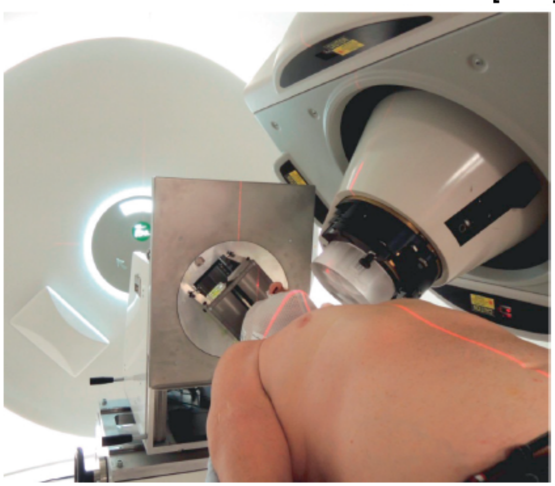


Fig. 1. PGI slit camera trolley (upper row) and its application during patient treatment (lower row).

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ELSEVIER

Original article

First clinical application of a prompt gamma based *in vivo* proton range verification system

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