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INTRODUCTION TO HADRON THERAPY

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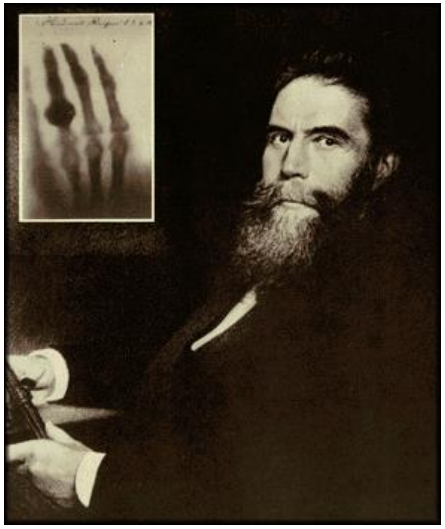
Outline

- ✓ HISTORY OF HADRON THERAPY
- ✓ PHYSICAL BASICS
- ✓ BIOLOGICAL BASICS
- ✓ TECHNICAL ASPECTS
- ✓ CONCLUSIONS AND FUTURE CHALLENGES

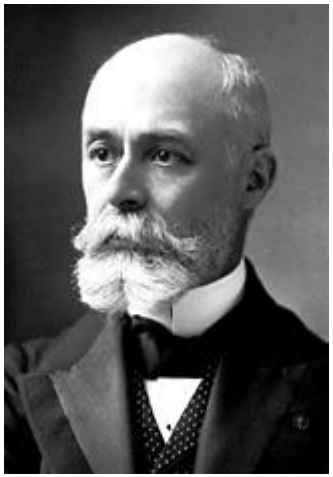
HISTORY OF HADRON THERAPY

1895: discovery of X rays

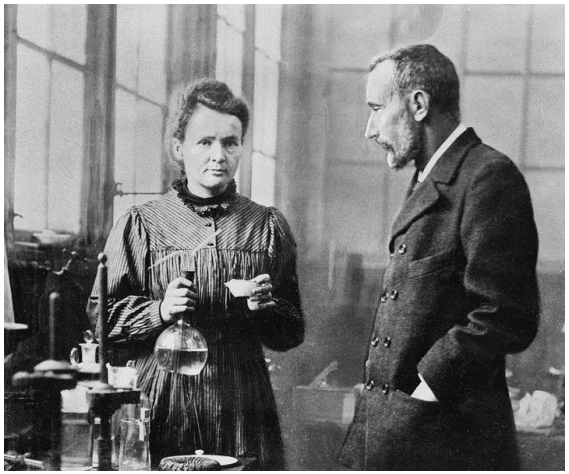


Wilhelm Roentgen

1898: discovery of radioactivity

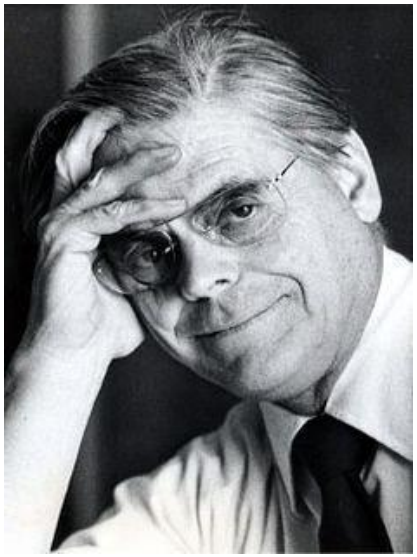


Henri Becquerel



Pierre and Marie Curie

HISTORY OF HADRON THERAPY



Robert Rathbun Wilson

1946: R. Wilson first proposed a possible therapeutic application of proton and ion beams

R. Wilson, Radiologial use of fast protons, Radiology 47, 487-491, 1946

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 large part, been due to the very short penetration in tissue of protons, deuterons

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 within the body, with but little skin dose. It will be easy to produce well

1954: first patient treated with deuteron and helium beams at Lawrence Berkeley Laboratory (LBL)

HISTORY OF HADRON THERAPY

The first hadron therapy centers operated at the nuclear and subnuclear physics laboratories:

- 1957: Uppsala (Sweden);
- 1961: Massachusetts General Hospital and Harvard Cyclotron Laboratory (USA);
- 1967: Dubna (Russia);
- 1979: Chiba (Japan);
- 1985: Villigen (Switzerland).

LLUMC (California, USA)

<u>1990</u>: the <u>first hospital-based proton therapy facility</u> at *Loma Linda University Medical Center* (LLUMC).

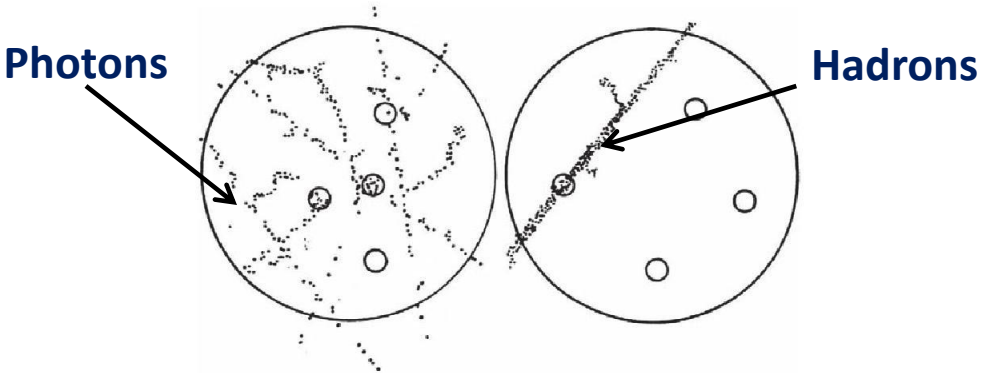
PHYSICAL BASICS

Hadron Therapy

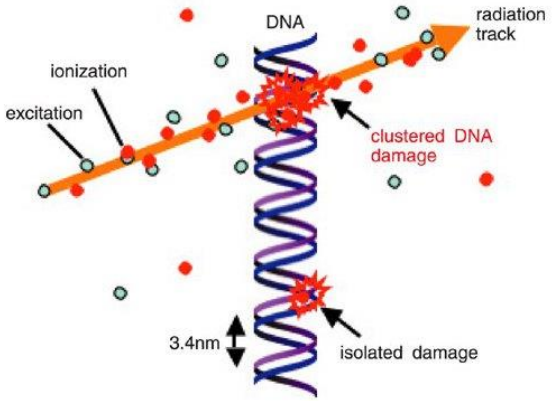
Treatment of tumors through external irradiation by means of accelerated hadronic particles:
neutrons, **protons**, pions, antiprotons, **helium**, lithium, boron, **carbon** and oxygen ions.

Protons and **heavy ions** (particles with mass greater than helium) have **physical properties**, and so **radiobiological effects**, such that:

1. **high and conformal dose is delivered to the tumor target;**
2. **minimazing the irradiation of healthy tissue.**



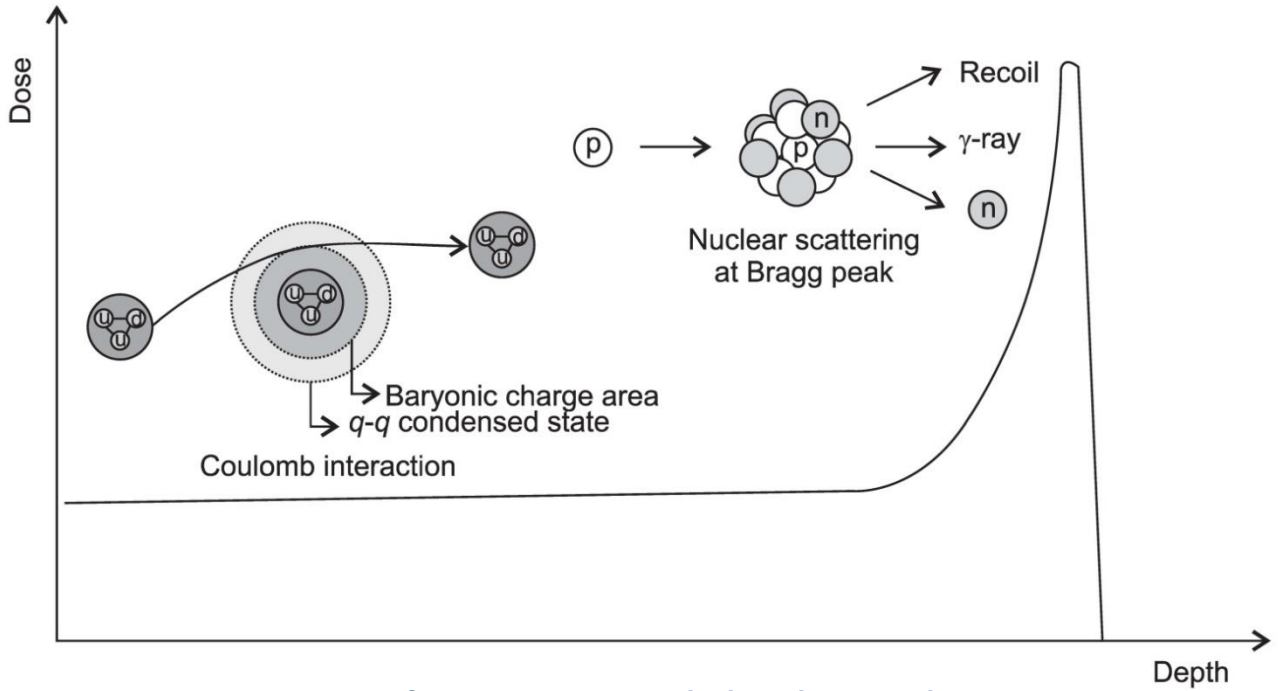
Ionization density



Effect on cellular DNA

PHYSICAL BASICS

Interactions of protons with biological matter



Interactions of protons with biological matter

Seo Hyun Park, Jin Oh Kang, *Basis of particle therapy I*:, *physis,* Radiat. Onol. J 29(3), 135-146, 2011

PHYSICAL BASICS

Interactions of protons with biological matter

Energy transfer relies mainly on:

➢ **Coulomb interactions** **(Stopping)** with the **outer-shell electrons** of the target atoms **-> excitation and ionization of atoms -> protons slow down - > energy loss** (80 ÷ 90%)

- loss per interaction small **-> continuously slow down**
- secondary electrons have range < 1mm **-> dose absorbed locally**

Energy loss is given by **Bethe-Bloch equation:**

$$-\frac{dE}{dx} = Kz^2\frac{Z}{A}\frac{1}{\beta^2}\left[\frac{1}{2}\ln\frac{2m_e c^2\beta^2\gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2}\right]$$

ze	Charge of incident particle
Z	Atomic number of absorber
A	Atomic mass of absorber

K/A	$4\pi N_A r_e^2 m_e c^2/A$
T_{max}	max energy transfer to free electron
I	Mean excitation energy

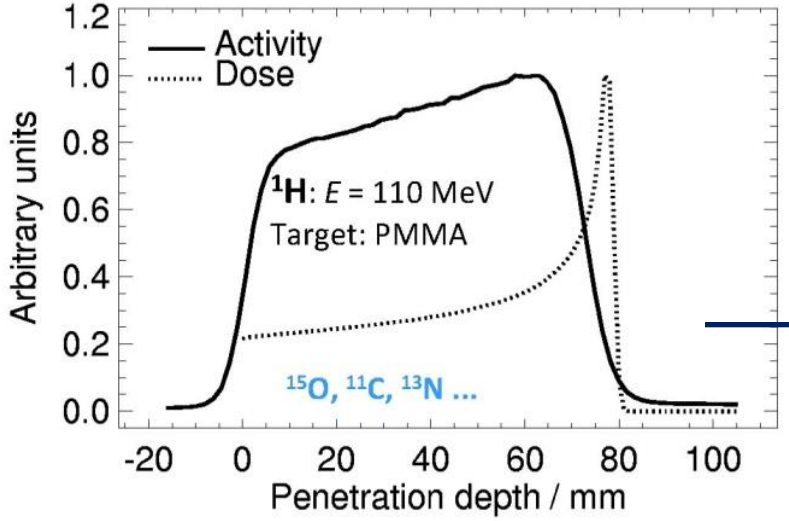
PHYSICAL BASICS

Interactions of protons with biological matter

➢ **Nuclear reactions:** **nonelastic nuclear reactions** with the target nuclei (energy loss 5 ÷ 20%) **->** production of secondaries such as

• protons, α ,recoils nuclei, γ-rays (nuclei excitation),
neutrons -> radiation safety

• **radioactive isotopes** (**tissue activation**), es. ^{15}O, ^{11}C, ^{13}N **(β^+-emitters**) **->** from isotopes activity 3D **dose verification** with PET/CT



K. Parodi et al., IEEE MIC CR, 2002

Proton beam @ 110 MeV

PHYSICAL BASICS

Interactions of protons with biological matter

Angular deflection of hadrons is due to

- **Multiple Coulomb Scattering (MCS): elastic Coulomb interactions** with the target nuclei -> superposition of small deflections **-> beam lateral penumbra (important for its effect on ograns at risk)**

Proton mass >> electron mass **->** deflections for elastic collisions can be neglected

MCS is well described from Moliére theory

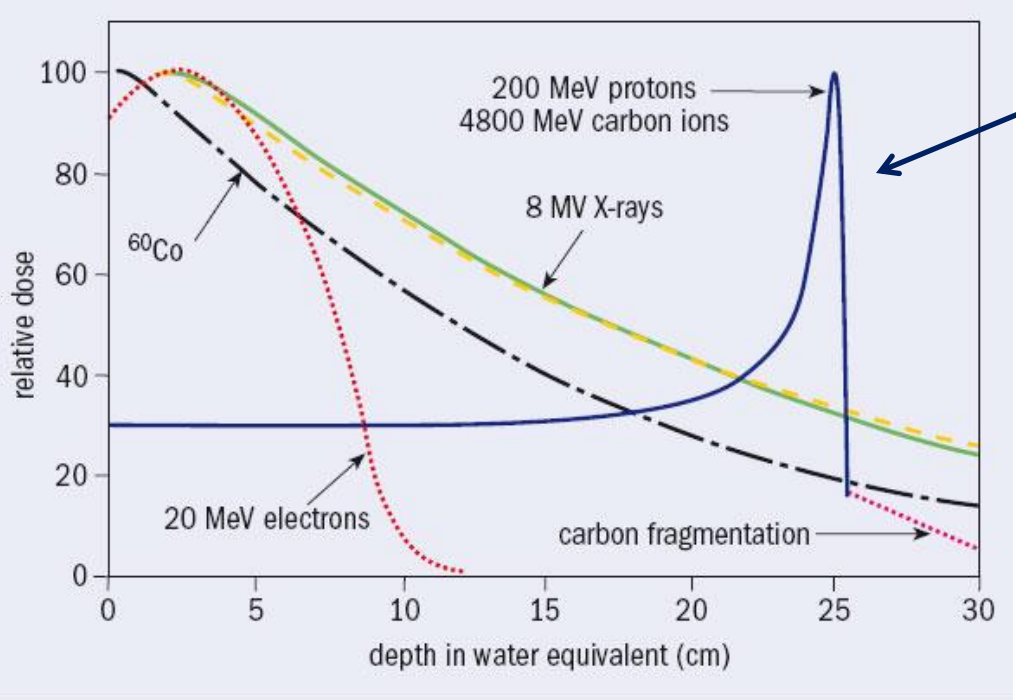
$$\theta_0 = \frac{14.1\ \text{MeV}}{pv}\, z \sqrt{\frac{L}{L_R}} \left[1 + \frac{1}{9} \log_{10}\left(\frac{L}{L_R}\right)\right]$$

p	proton momentum	L	target thickness
v	proton speed	L_R	target radiation length

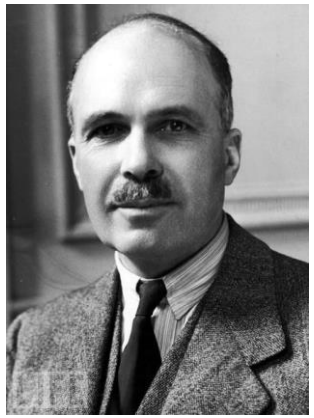
Lateral scattering can be approximately described with a **Gauss distribution.**

PHYSICAL BASICS

Depth-dose curve



Bragg peak



William Bragg

Physical absorbed dose

$$Dose = \frac{dE}{dm} \quad [Gy = J/kg]$$

Dose: [40 Gy, 70 Gy]

$$-\frac{dE}{dx} \propto V^{-2}$$

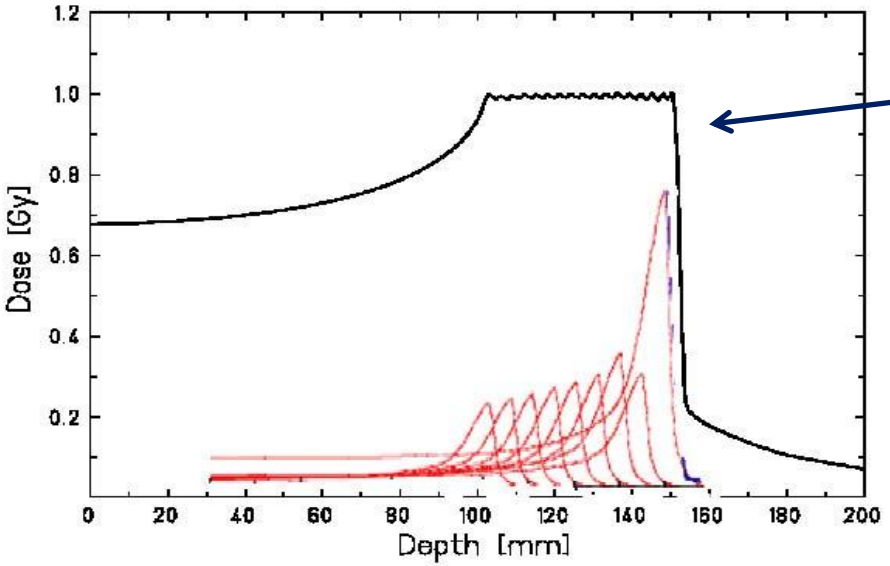
the highest dose is released near the end of hadron range giving rise to the "Bragg peak"

Range: penetration depth such that dose absorbed is 80% of peak value

Range and dose distribution calculation must be as accurate as possible

PHYSICAL BASICS

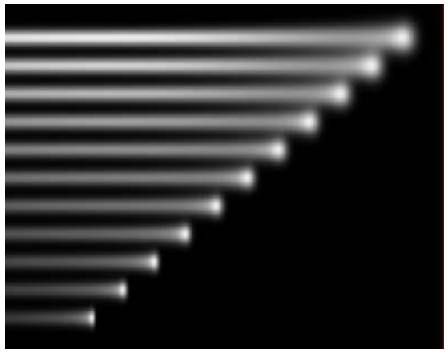
Spread-out of Bragg Peak (SOBP)



SOBP

To treat an extended target the Bragg peak is spread out to cover the whole volume by modulating the beam energy

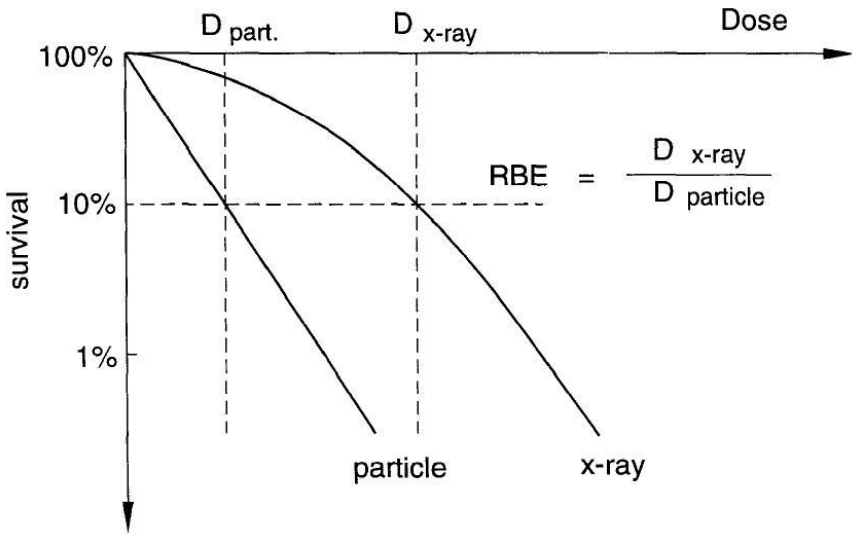
Beam energy modulation



BIOLOGICAL BASICS

Relative Biological Effectiveness (RBE)

$$RBE = \frac{D_{X\text{-rays}}}{D_{particle}}$$



RBE depens on many factors:

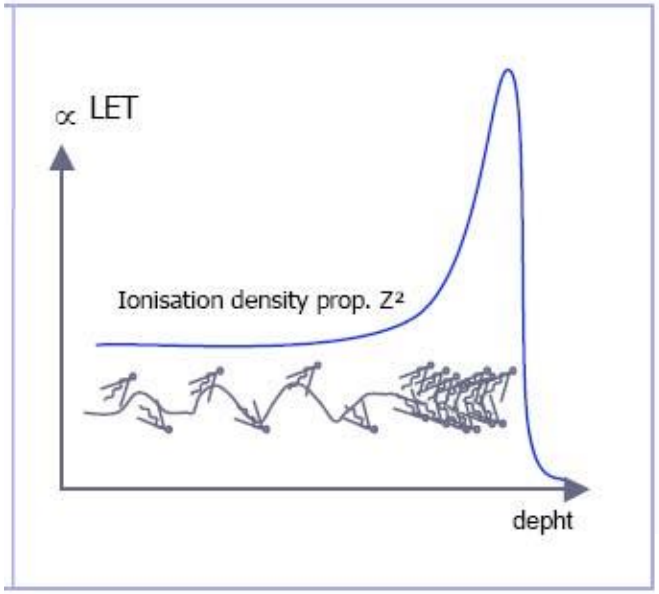
- energy;
- particle type;
- organ dimensions;
- tissue type;
- presence of oxygen.

hadrons more biologically effective than photons: lower dose is required to cause the same biological effect

BIOLOGICAL BASICS

Linear Energy Transfer (LET)

$$LET = \frac{dE}{dl} \quad [keV/\mu m]$$

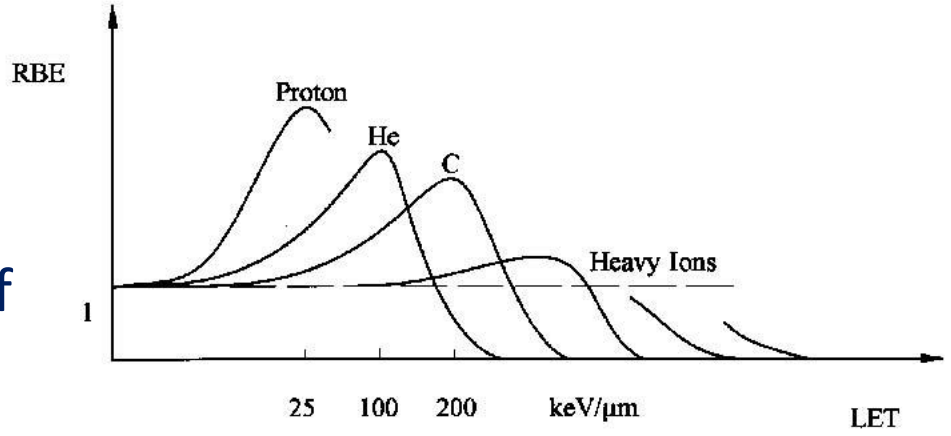


LET -> ionization density -> quality of radiation

High LET (> 10 keV/µm) -> multiple DNA damages

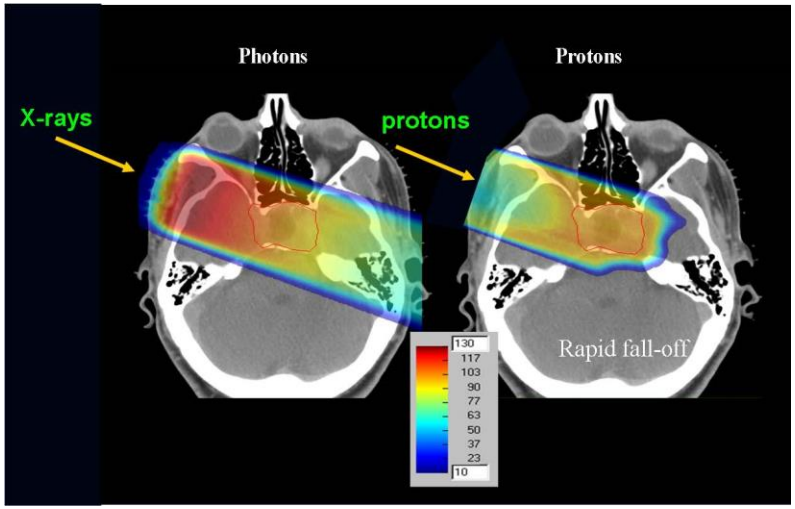
Hadrons are high LET with respect to photons

Relationship between RBE and LET as a function of particle type



BIOLOGICAL BASICS

Protons vs photons



TC image: dose distribution calculated for proton beams and X-rays.

Physical advantages :

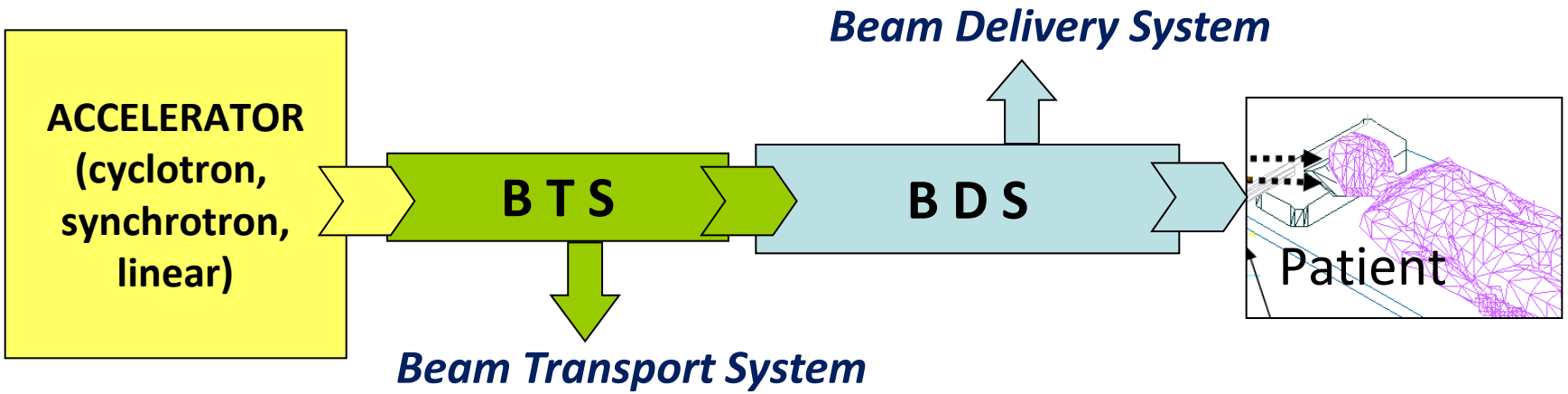
- ✓ finite range and high ionization density;
- ✓ lower integral dose;
- ✓ small lateral scattering (larger flexibility).

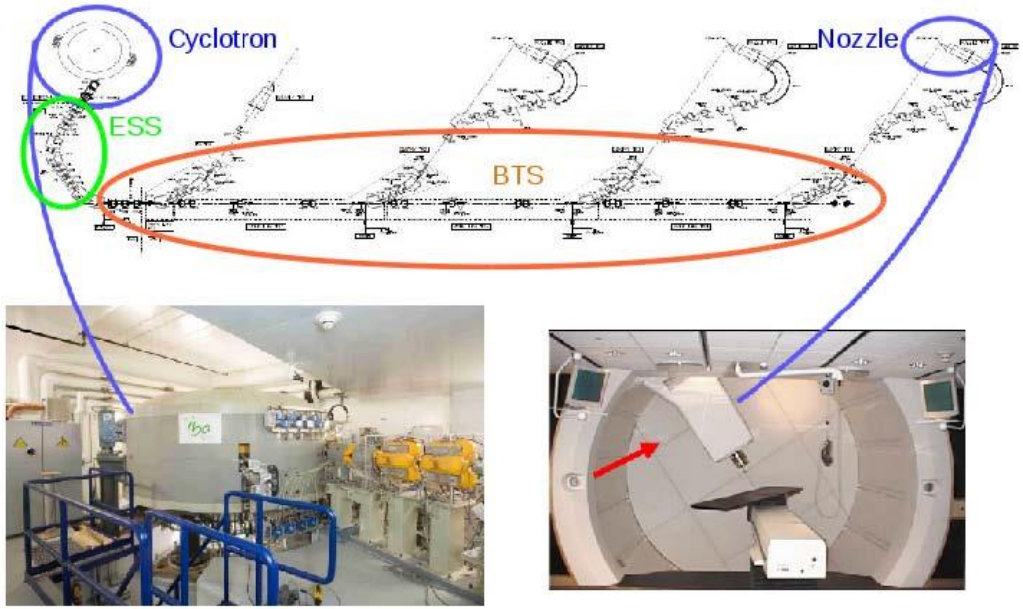
Clinical advantages :

- ✓ treatment of deep-seated, irregular shaped and radioresistant tumors;
- ✓ small probability of side effects in normal tissue (critical structrure);
- ✓ proton therapy suitable for pediatric diseases (reduced toxicity).

TECHNICAL ASPECTS

Main parts of an hadron therapy facility

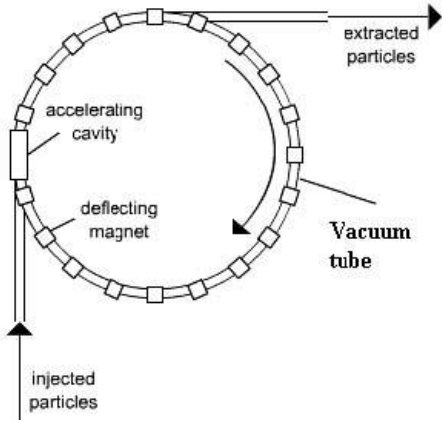




Hadron therapy facility scheme – IBA (Belgium)

TECHNICAL ASPECTS

Particle accelerators



Synchrotron: presents a cycle (spill) that lasts about 2 s, beam is present for about 0.5 s and its energy can be varied from spill to spill without passive elements.

Energy range for therapeutic hadron beams:

- **p: [60, 250] MeV**
- **^{12}C: [120, 400] MeV/u**

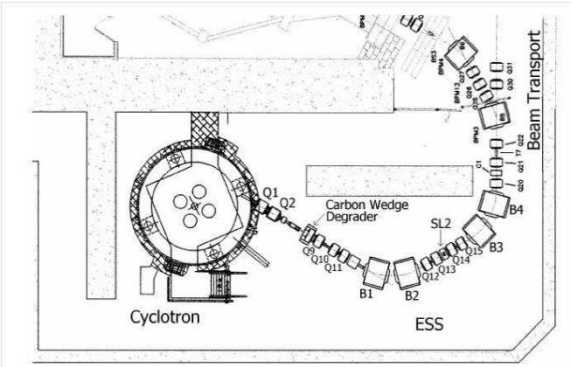
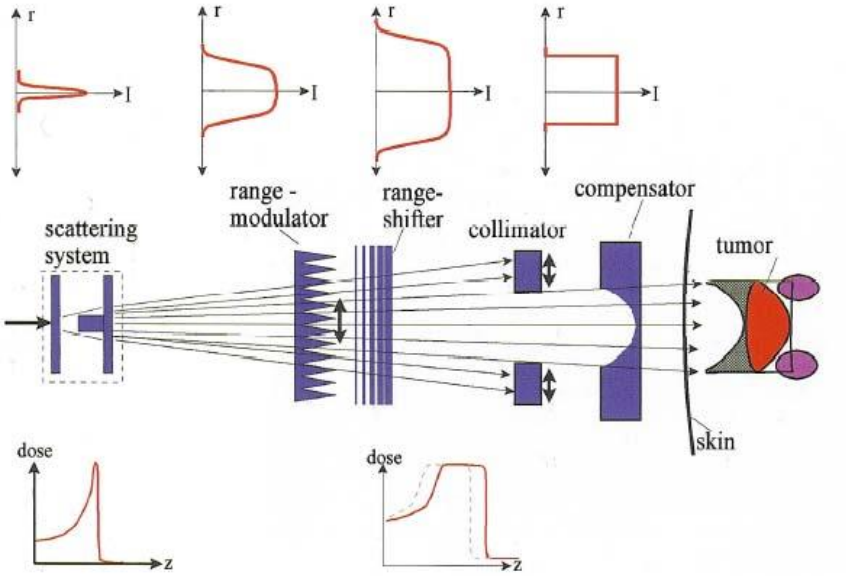


fig. 1. Detail of the Energy Selection System (ESS) showing the location of the carbon energy degrader and the momentum spread limiting slit (SL2).

Cyclotron: high intensity, continuous beam, its energy is fixed and can be degraded with passive absorbers in the Energy Selection System (ESS).

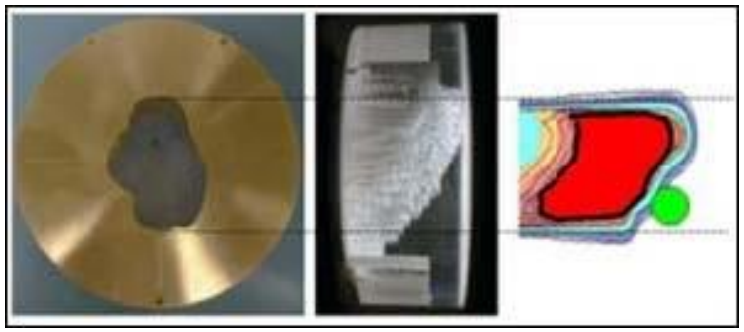
TECHNICAL ASPECTS

Beam Delivery System – Passive Scattering System



Passive Scattering System

Beam is widened and flattened by means of personalized collimators and compensators. Range shifter (rotating wheel with different thickness) is used to irradiate at different penetration depths (SOBP).

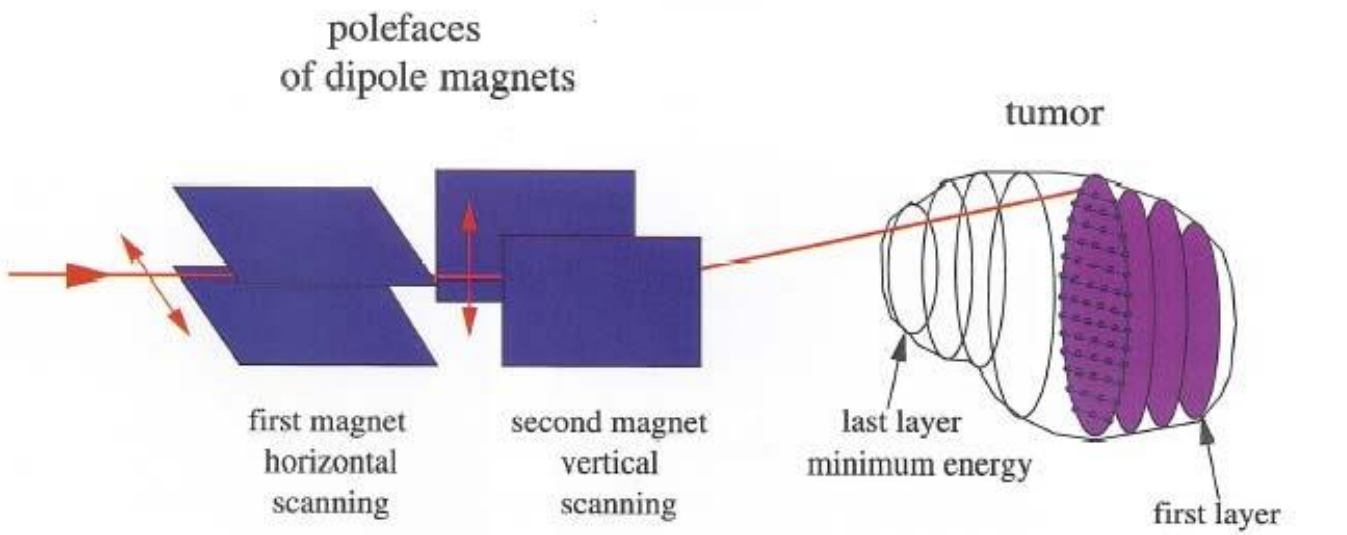


Collimator and compensator

Range Modulator

TECHNICAL ASPECTS

Beam delivery system – Active Scanning System



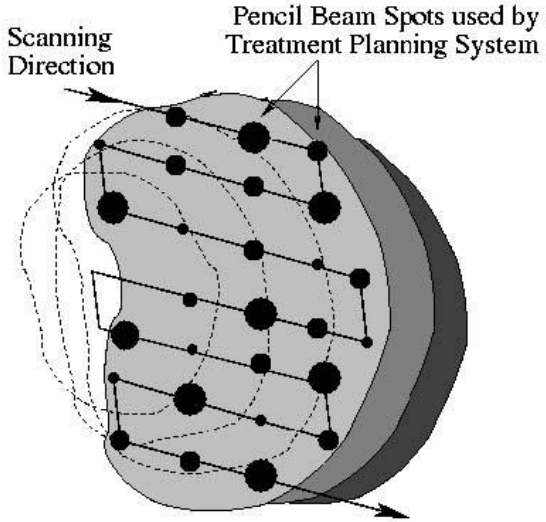
Active Scanning System

✓ Hadrons can be deflected magnetically **->** a narrow mono-energetic **"pencil beam"** can be scanned magnetically across the target volume in a zigzag pattern in the x-y plane perpendicular to the beam direction (z);

✓ the depth scan is done by means of energy variation.

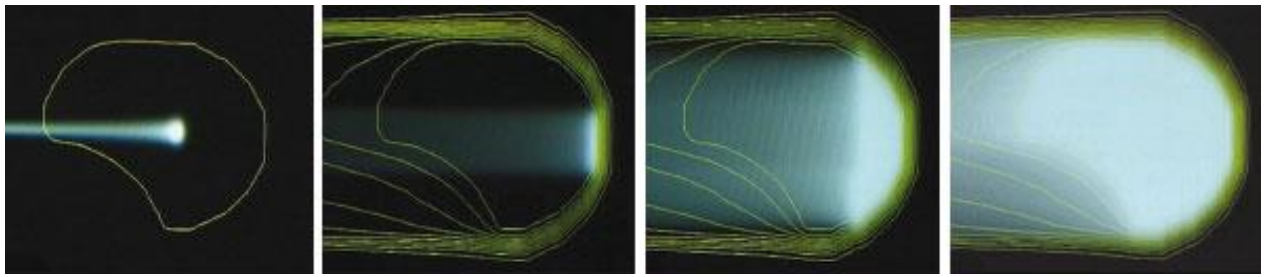
TECHNICAL ASPECTS

Dose delivery system – Active Scanning System



Principle of active beam scanning

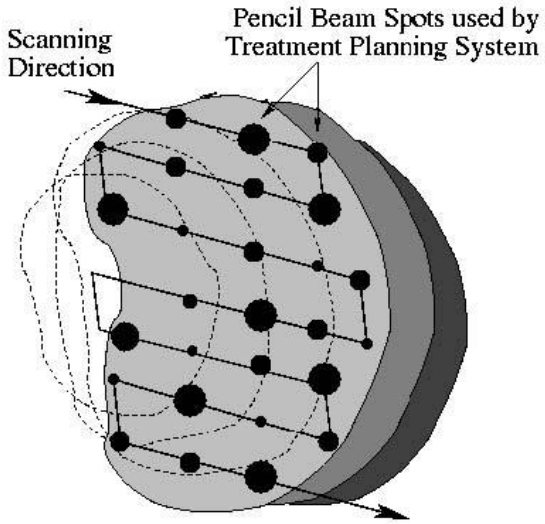
Discrete spot scanning: (developed at **PSI**) dose is delivered to a given spot at a static position (constant magnet settings). Then the pencil beam is switched off and the magnet settings are changed to target the next spot, dose is delivered to the next spot, and so forth.



Single beam | **Lateral scanning** | **Scanning in depth** | **3D dose distribution**

TECHNICAL ASPECTS

Dose delivery system – Active Scanning System



Principle of active beam scanning

Raster scanning: (developed at **GSI** - Darmstadt) continuous path, beam dose not switch off between two voxels (except two spot are away from each other).

Dynamic spot scanning: beam is scanned fully continuously across the target volume. Intensity modulation can be achieved through a modulation of the output of the source, or the speed of the scan, or both.

TECHNICAL ASPECTS

Active Scanning System vs Passive Scattering System

Advantages of Active Scanning technique:

1. No need of compensators and collimators (dependent on patient anatomy), the beam has less nuclear interactions outside the patient, this means **less neutron contamination and overdose**;

2. great flexibility, arbitrary shapes can be irradiated with a single beam, this allows **better target conformation**.

Disadvantage of Active Scanning technique:

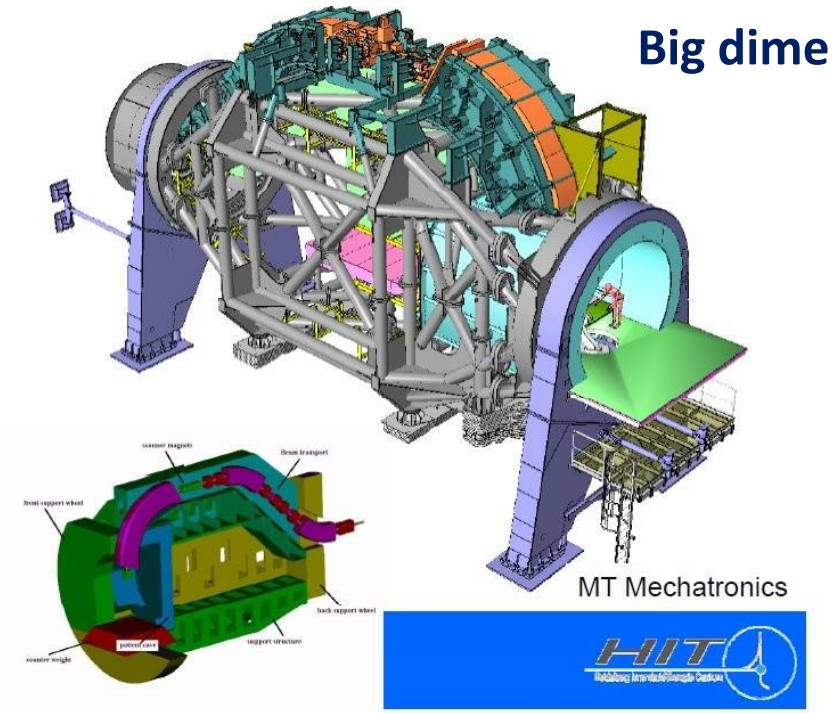
1. **Difficulty to treat "*moving organs*"** (organs subject to motion due to respiration) such as lung cancer, it is necessary to develop systems to synchronize the beam and the patient's respiration.

TECHNICAL ASPECTS

Gantry and nozzle

Conformal radiation therapy requires target irradiation from any desired angle. The beam is deflected by the magnetic field in the **gantry**. Treatment **nozzle** (final part of the gantry) consists of various components for <u>beam shaping and beam monitoring.</u>

Big dimensions (3.5 m diameter) **-> very expensive**



Gantry at Hidelberg Ion-beam Therapy Center (HIT)

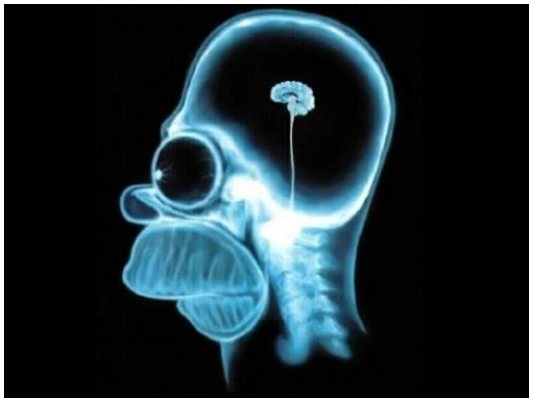
Treatment room at Boston Northeast Proton Therapy Center (NPTC)

TECHNICAL ASPECTS

Imaging and quality assurance

Computed Tomography (CT) / Positron Emission Tomography (PET) essential:

- prior to treatment-planning for delineating target volumes and structures of interest;
- to position and immobilize the patient reducing errors;
- online and offline monitoring (*in vivo* 3D dose and/or range verification).



Homer Simpson CT

All sources of uncertainties must be minimize:

- test for mechanical and electrical safety;
- test of beam characteristics (intensity, profile and position must be stable);
- check of tolerances and geometric misalignments;
- shielding for secondary radiation (specially neutrons).

TECHNICAL ASPECTS

Monte Carlo Simulations

Monte Carlo method: probabilistic method that allows to solve analytically complex problems, stochastic or deterministic, by means of sampling techniques.

MCS "gold standard" in radiation therapy for:

- ✓ dose distribution prediction;
- ✓ range uncertainties estimation;

} treatment planning validation

- ✓ radiobilogical studies;
- ✓ design an commissioning of facilities.

Accurate results require the simulation of a large number of events ($10^6 \div 10^9$) -> long execution time and large computational resources

GRID computing

TECHNICAL ASPECTS

Hadron therapy facility in Itlaly

CATANA (Centro di Adroterapia e Applicazioni Nucleari Avanzate) @ LNS (Laboratori Nazionali del Sud) - Catania

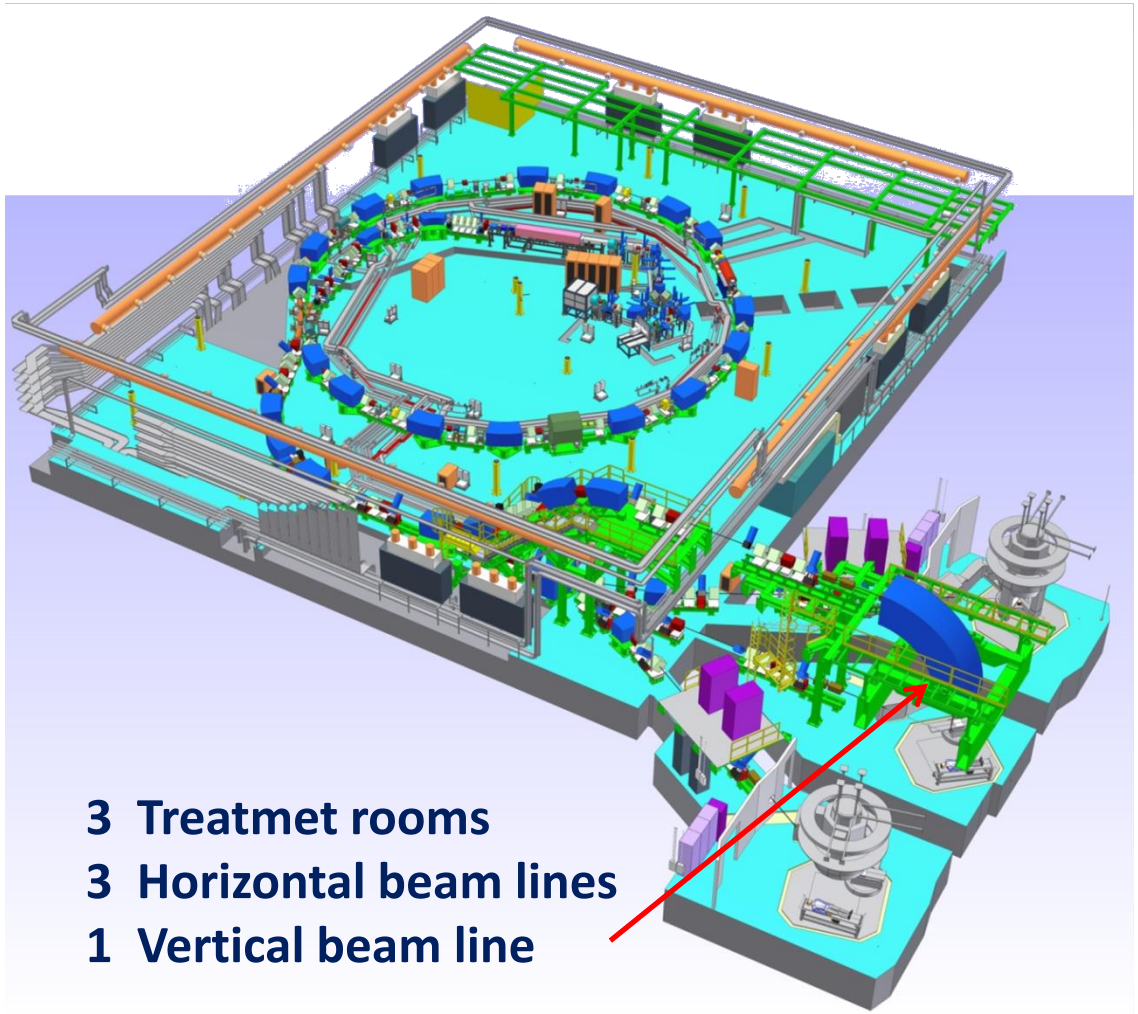
CATANA treatment room

Since 2002 eye tumors are successfully treated with proton beams of 62 MeV produced by a superconducting cyclotron (SC).

TECHNICAL ASPECTS

Hadron therapy facility in Itlaly

CNAO (Centro Nazionale di Adroterapia Oncologica) @ Pavia



- Treatments with protons started in september 2011
- Treatments with carbon ions started in november 2012

p E : [60, 250] MeV

C^{6+} E : [120, 400] MeV/u

Syncrotron
(26 m diameter)

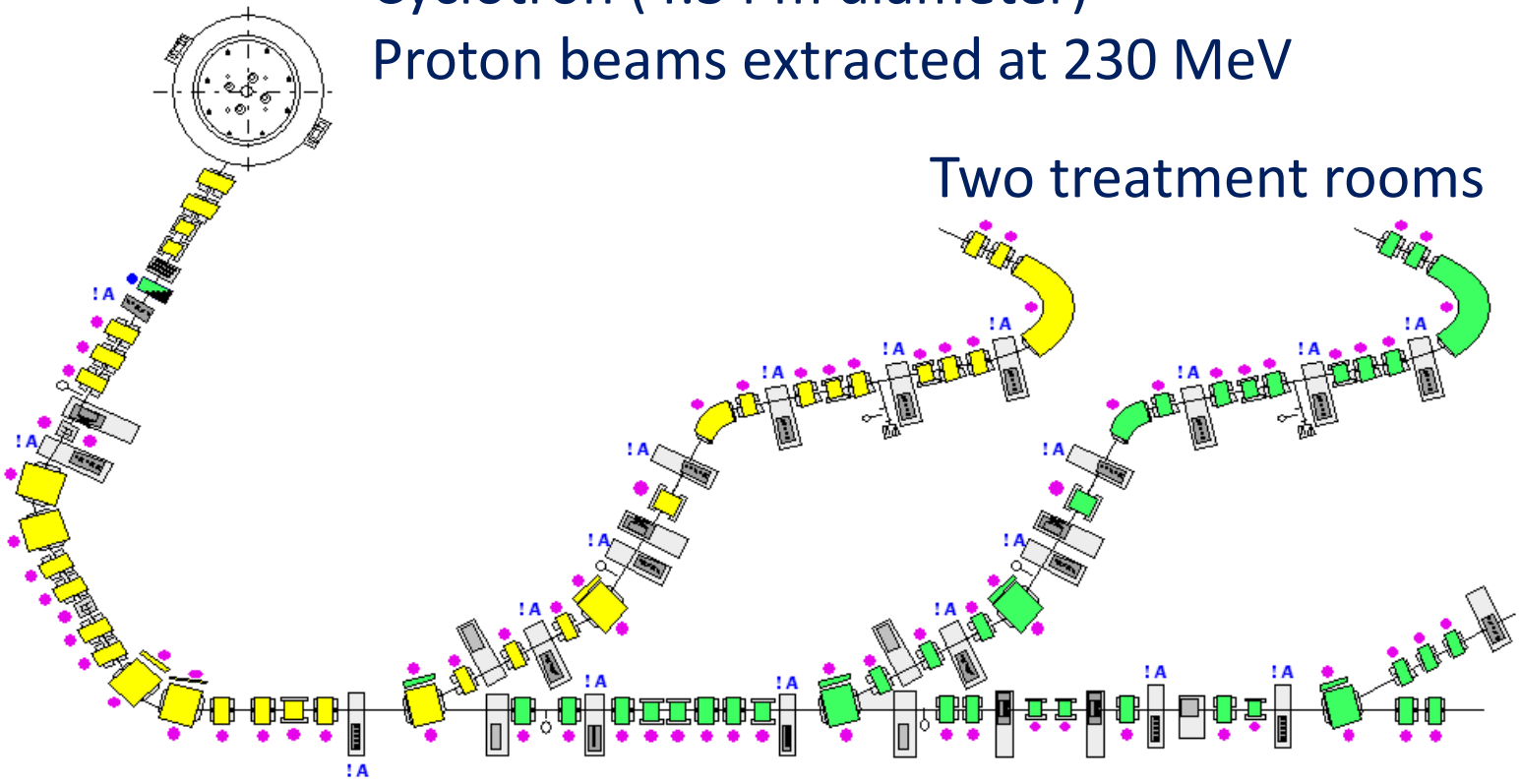
TECHNICAL ASPECTS

Hadron therapy facility in Itlaly

ATreP (Agenzia Provinciale per la Protonterapia) @ Trento

Cyclotron (4.34 m diameter)
Proton beams extracted at 230 MeV

Two treatment rooms



Inaugurated in July 2013, after commissioning it's starting the clinical activity

CONCLUSIONS AND FUTURE CHALLENGES

Hadron therapy reperesents an important instrument for the cure of cancer;

it can be considered the direct application of high energy physics research and technologies developed for the experiments;

it's a multidisciplinary field (medicine, physics, biology, engineering) in continuous evolution.

Research and development efforts**:**

to improve carbon ion treatment and introduce new hadrons (helimun ions);

to improve beam delivery techniques and moving organs treatment;

to construct new accelerators (LINAC or laser plasma accelerator).

THANKS FOR YOUR ATTENTION

P.R. Altieri: palma.altieri@ba.infn.it

BACK UP

PHYSICAL BASICS

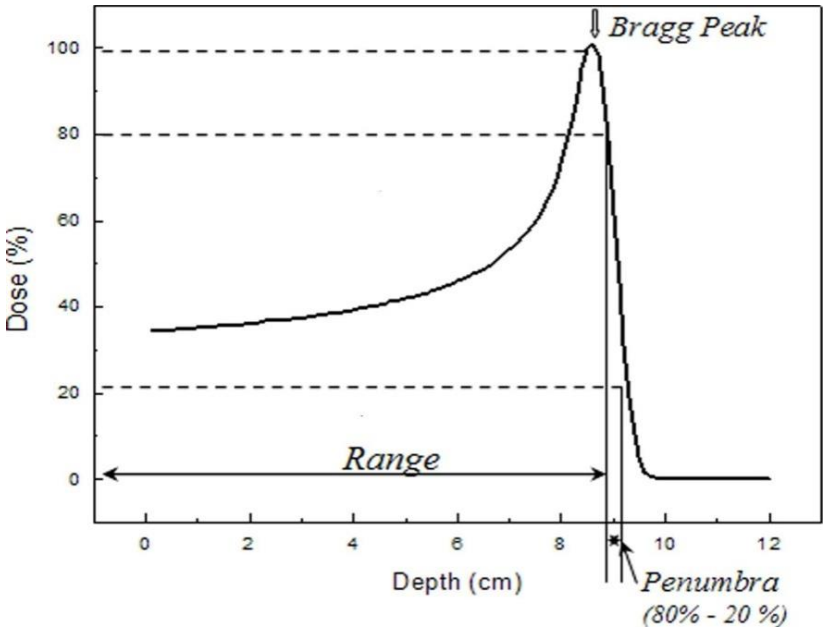
Absorbed dose

$$Dose = \frac{dE}{dm} \quad [Gy = J/kg]$$

Ideal dose distribution:
- 100% to the target
- 0% to surrounding healthy tissue

Fluence

$$\Phi = \frac{dN}{dA} \quad [Particles/cm^2]$$



Range: penetration depth such that dose absorbed is 80% of peak value.