Research for Radiotherapy with Hadrons

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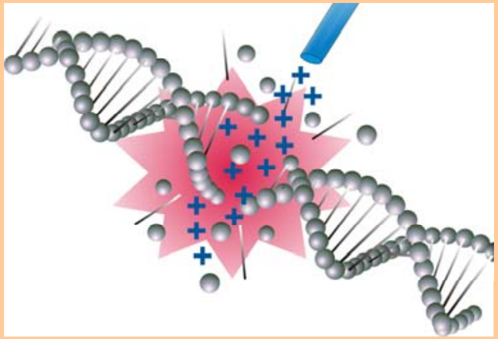
The secret of modern radiotherapy is to place the beam on the target with the desired dose while sparing normal tissue.

Rapid technological progress in recent years has led to an evolution in all areas of medicine and has significantly influenced radiation oncology.

Radiotherapy is the process of irradiating a malignant tumour using ionizing radiation with the aim of damaging the DNA of the cancer cells.

Low ionizing radiation: Photons (X-rays, γ-rays)
High ionizing radiation: Protons, ^{12}C ions

Today, a new frontier in radiation therapy is represented by the *Hadrontherapy*, which is *the use of protons and atomic nuclei (ions) called hadrons* (from the Greek hadrós, strong) that are subjected to a strong nuclear force.



Currently about 45% of cancer cases can be treated, mainly by surgery and/ or by radiation therapy.

Hadrontherapy with protons and carbon ions is the second best technique, surpassed only by surgery. Up to the middle of the first decade of the new millenium, about 40.000 patients worldwide were treated by particle therapy at 22 particle therapy centers (Europe, USA, Japan, China, South Africa). The number of treated patients is increasing constantly.

Treatment room at the Heidelberg Ion Therapy Centre.
Image credit: GSI/HIT/Siemens.Heilderberg

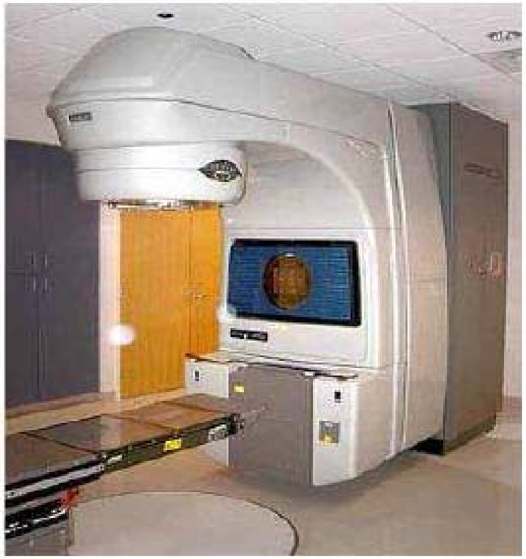
Treatment room at CNAO, Pavia, Italy.

Hadrontherapy

- HT = Radiotherapy (RT) using protons and ion beams

About half of all people with cancer are treated with radiation therapy, either alone or in combination with other types of cancer treatment
NCI – National Cancer Institute

- The term of comparison for hadron-therapy: Conventional radiotherapy (RT) with photons
  - Gone through a very strong modernization
    - CT-based computerized treatment planning
    - New dynamic beam delivery techniques
      - Intensity Modulated RT (IMRT)
      - Tomotherapy
    - Recently – Treatment of moving tumors
      - Respiration gated irradiation
      - 4d-CT and 4d-MRI (time resolved images)
    - Image-guided radiotherapy (images for positioning adaptation on line)



Ernest Lawrence invented the cyclotron (1930)

For a charged particle moving in a perpendicular magnetic field:

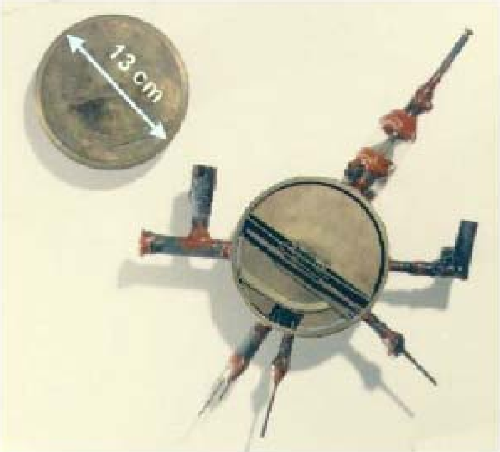
$a_{centripetal} = evB/mc$ e moving in B

$a_{centrifugal} = v^2/r$ mechanical centrifugal acceleration

$v/r = eB/mc$ for a stable orbit (**The Cyclotron Equation**)

The Cyclotron Frequency

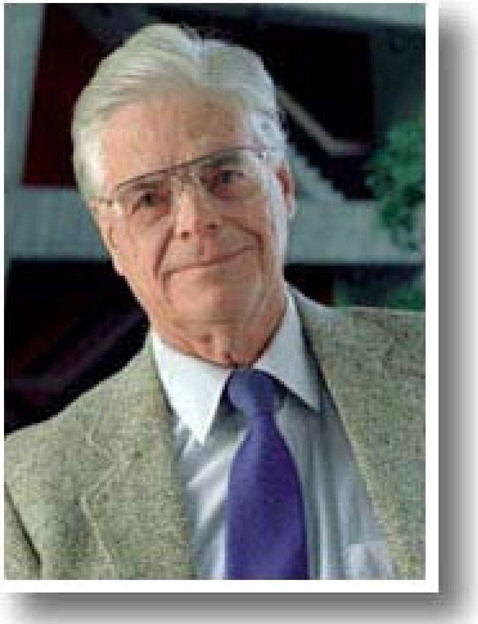
$f = v/2\pi r = eB/2\pi mc$ **independent of r !**



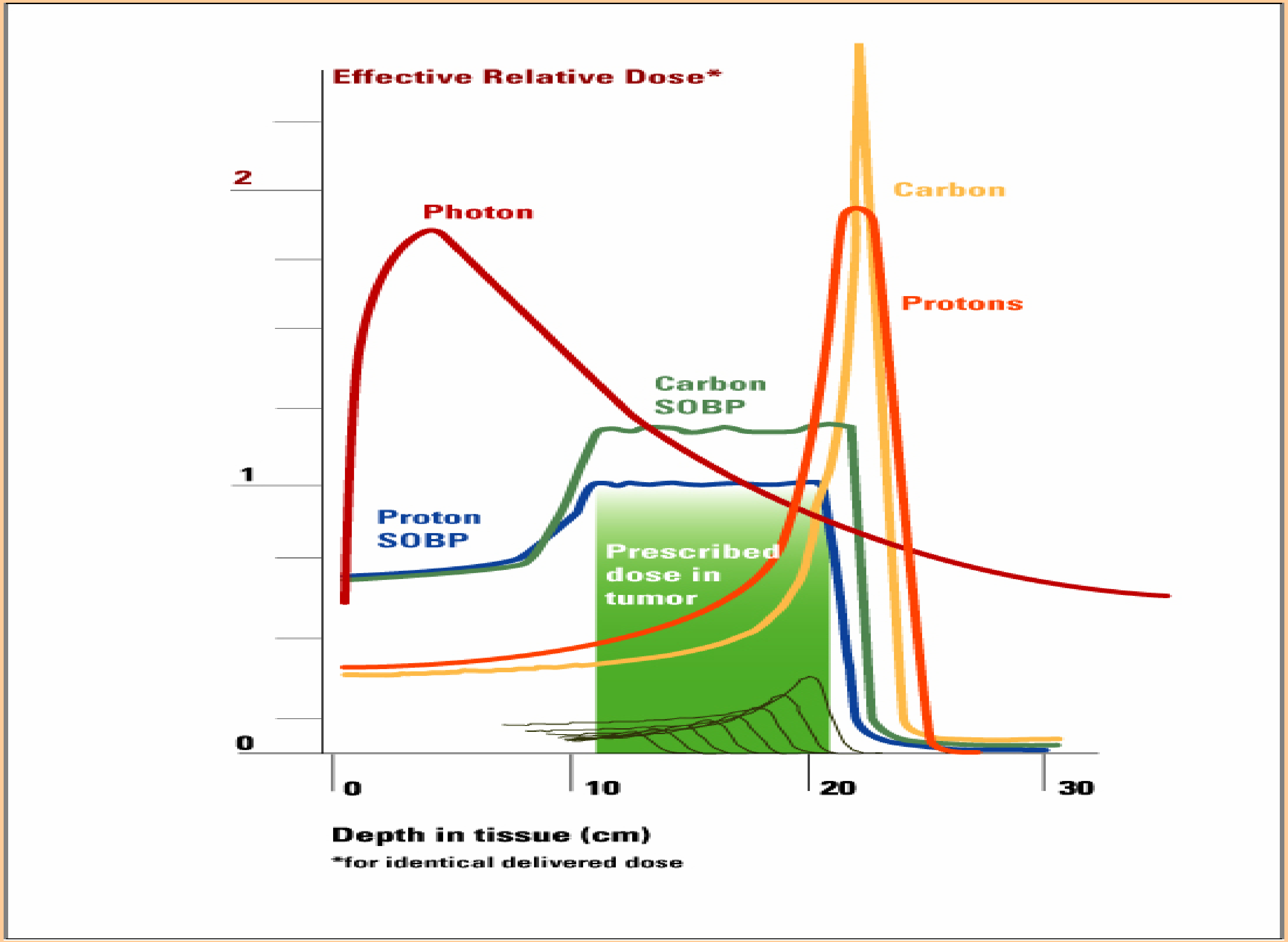
Lawrence, E.O. and Livingstone M.S., **Phys. Rev 37**: 1707 (1931); and Livingston, M.S., "The Production of High-Velocity Hydrogen Ions Without the Use of High Voltages," PhD thesis, University of California, Berkeley (1931).

A Man - A Vision

- In 1946 Harvard physicist Robert Wilson (1914-2000) suggested*:
  - **Protons can be used clinically**
  - **Accelerators are available**
  - **Maximum radiation dose can be placed into the tumor**
  - **Proton therapy provides sparing of normal tissues**
  - **Modulator wheels can spread narrow Bragg peak**


Robert Wilson

*Wilson, R.R. (1946), “Radiological use of fast protons,” Radiology 47, 487.

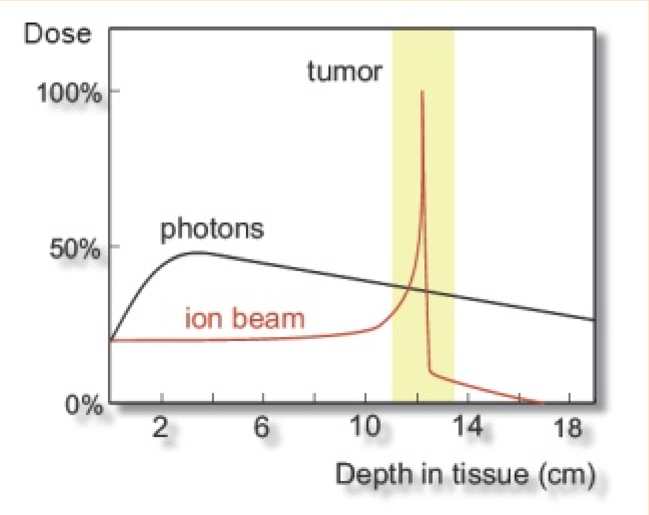


Crucial advantages of hadrons *vs.* conventional radiation:

- targeting radiation dose precisely into the tumour,
- sparing neighboring healthy tissue.

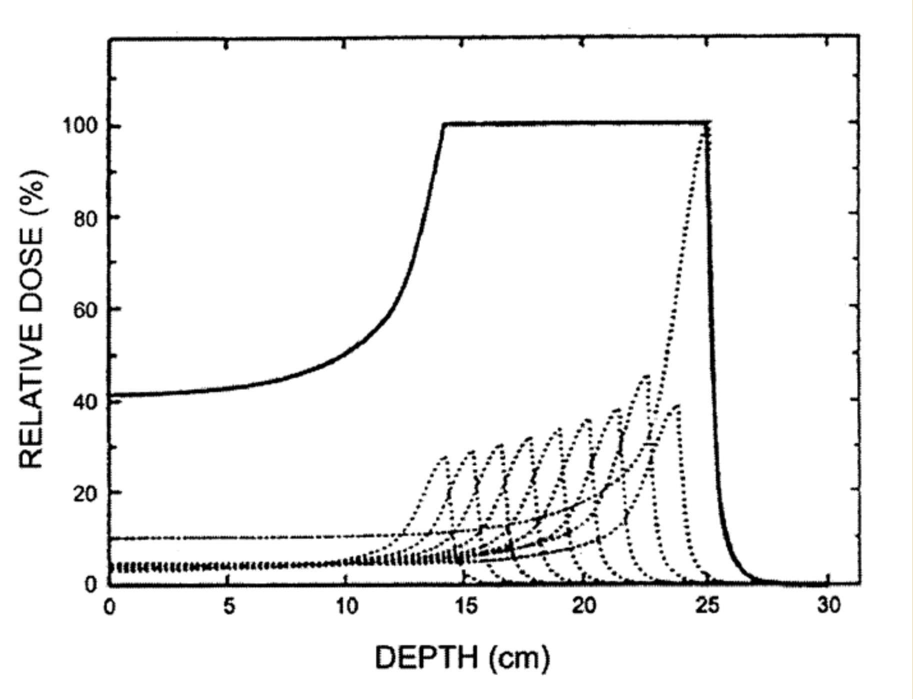
Physical qualities of hadrons:

• small lateral scattering,
• energy loss per unit length – linear energy transfer (LET) – increases while the hadron slows down,
• range directly proportional to energy,
• depth-dose distribution:
  - slow increase of dose – plateau region,
  - rapid build-up to a sharp maximum almost at the end of range – the Bragg peak,
  - distal swift fall-off.

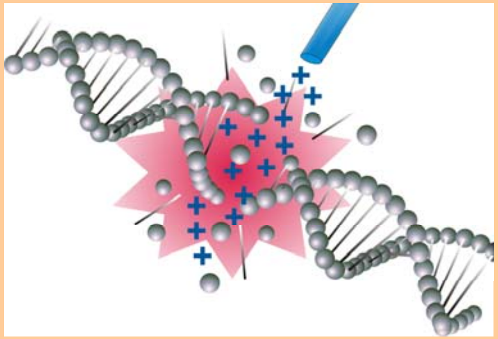


Practical approach – to deliver uniform dose over large volume at a given depth:

- Spread-out Bragg peak (SOBP) – modulation of hadron energy at the price of a slight increase of the entrance dose.
- Modulation of hadron energy, i.e., range, is achieved by degrading initial hadron energy which results in superimposition of a number of monoenergetic hadron beams of closely spaced energies, thus the position of the Bragg peak is pooled back towards the beam source as energy is reduced.
- The Bragg peak and SOBP have a higher LET than the beam entering the tissue.



- DNA is the principal target in radiobiology.
- Radiation interaction with DNA is a stochastic event.
- Single damages (break or base oxidation) are easily repaired.
- Clustered damages are difficult or impossible to repair.



Biologic effects

low LET

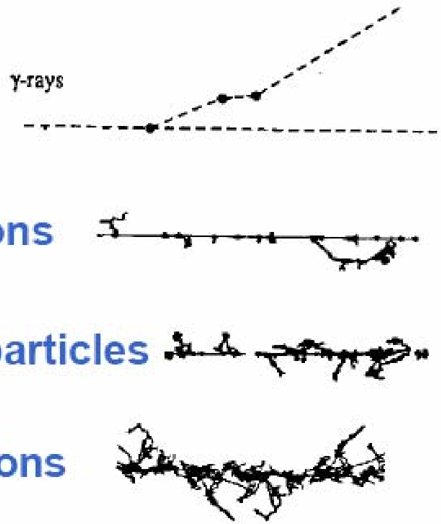
high LET

Photons

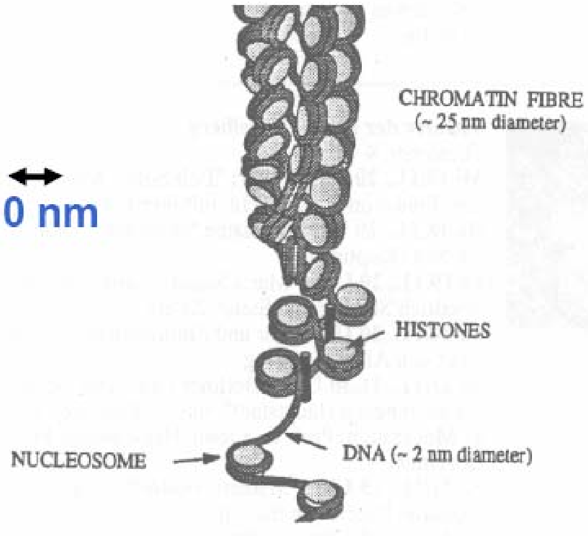
1 MeV protons

1 MeV/u α-particles

1 MeV/u C-ions



10 nm

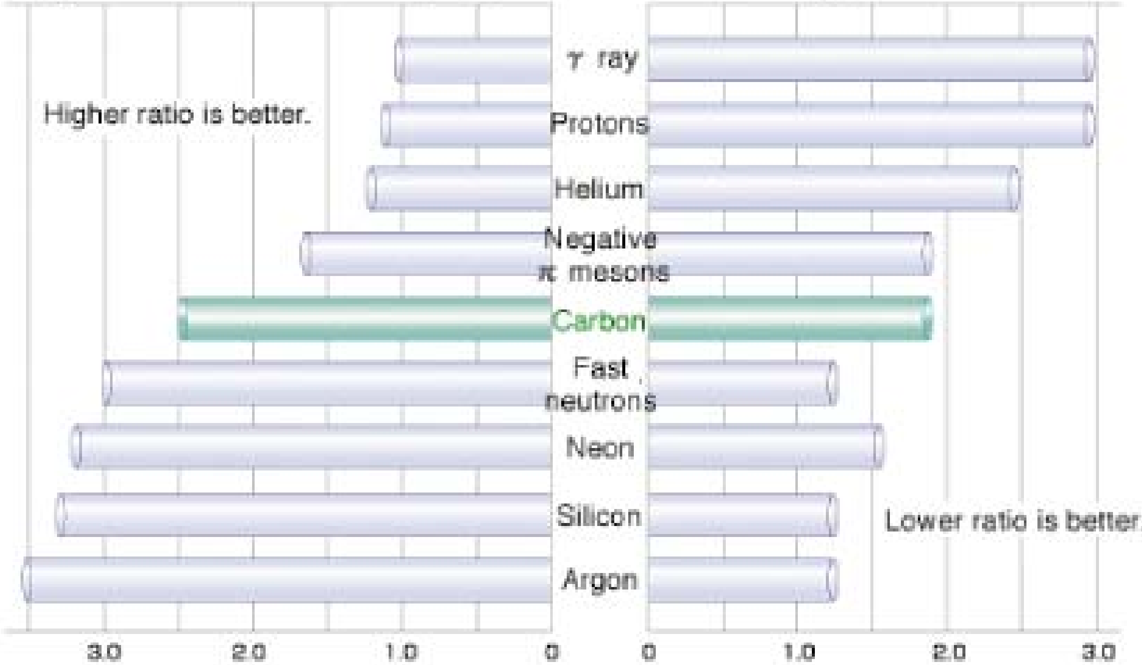


Kraft 1996

➡ elevated biologic effectiveness

3.Why Hadrons? Which Hadrons? (Cont)

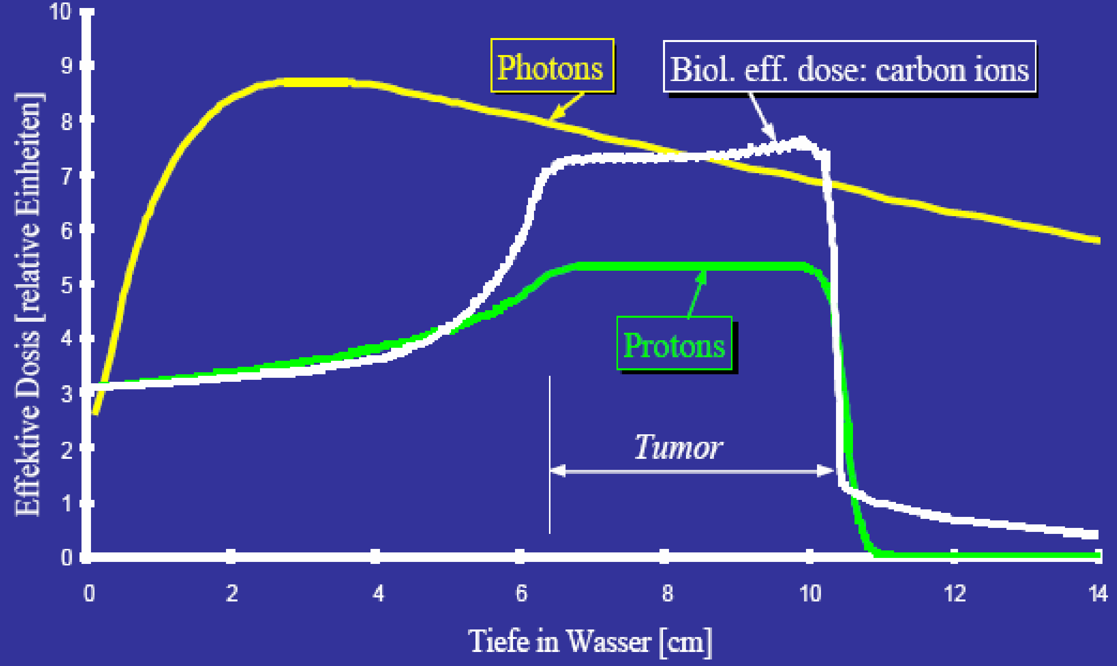
Relative biological effectiveness (RBE) and
oxygen enhancement ratio (OER) of various radiation types



RBE represents the biological effectiveness of radiation in the living body.
The larger the RBE, the greater the therapeutic effect on the cancer lesion.

OER represents the degree of sensitivity of hypoxic cancer cells to radiation.
The smaller the OER, the more effective the therapy for intractablecancer cells with low oxygen concentration.

Heavy ion therapy



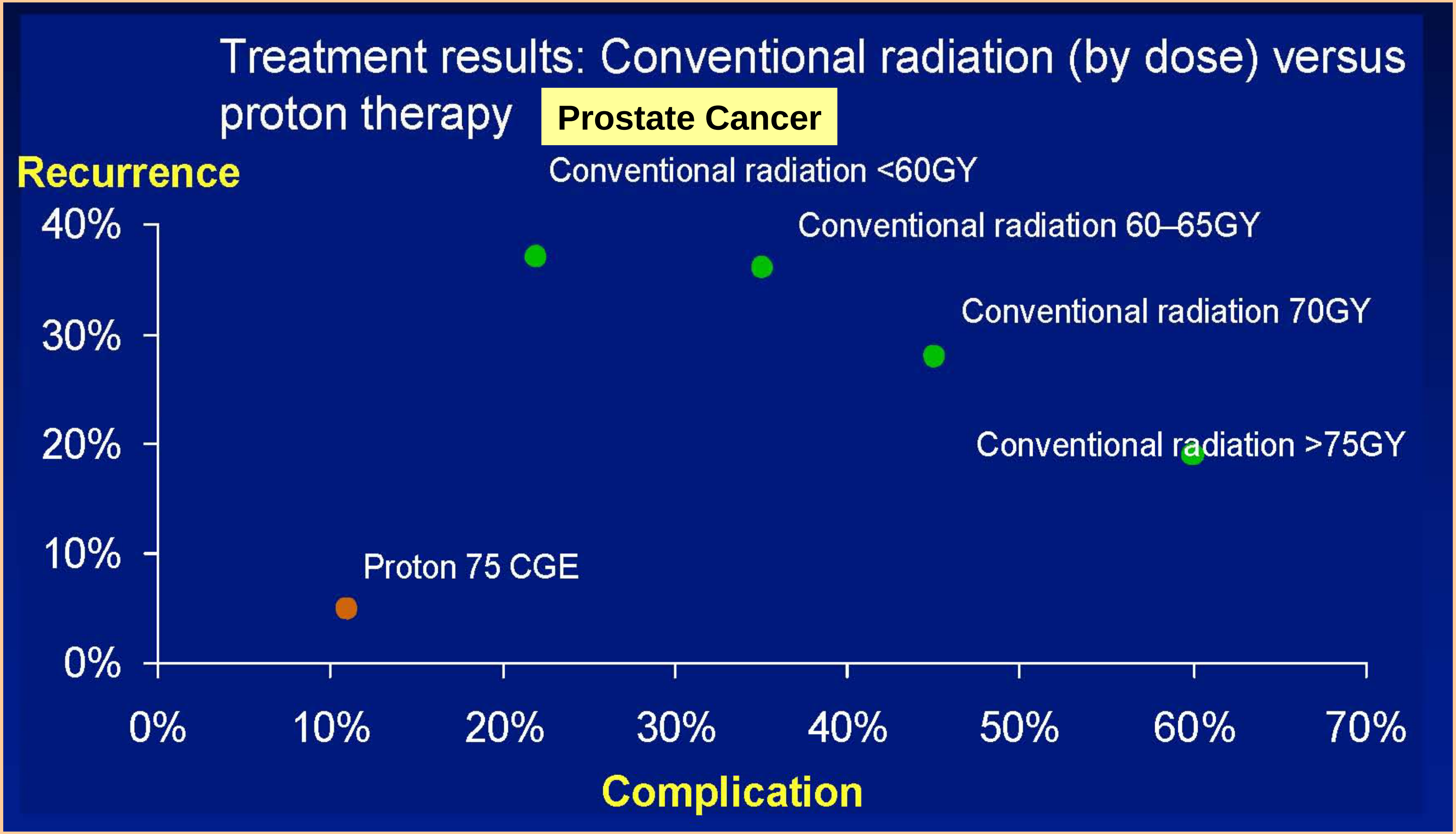
Advantages

- physical selectivity
- High-LET effect
- reduced integral dose

Disadvantages

- costs
- limited availability

Patient Monitoring, Follow-up and Trials

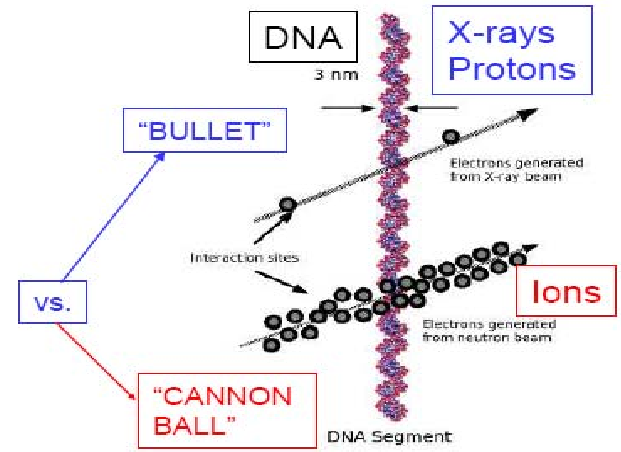


Loma Linda;
Presented by Ken Peach: Physics for Health, CERN, 2010

Radiobiology of heavier (light) ions
High LET of carbon ions

What is high-LET radiation ?

- LET (LET = Linear energy transfer – a way of saying "ionization density")
  - Relevant, the density of the ionization tracks at the size of the DNA structure
  - If LET low <u>at low doses</u> -> single damage to the DNA chain -> <u>Repair</u>
  - If LET high -> multiple damages to the DNA chain -> <u>NO repair</u>



- High LET: means
  - For the <u>tumor</u> cells
    - Increased efficiency of killing
  - For the <u>healthy tissues</u>
    - Increased "collateral damage"
      - Acute effects
      - Late effects
      - Secondary cancer induction
- Value controversial (needs more clinical trials)

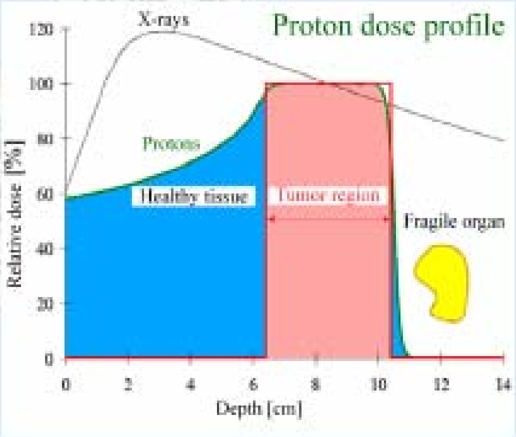
(a wikipedia image)

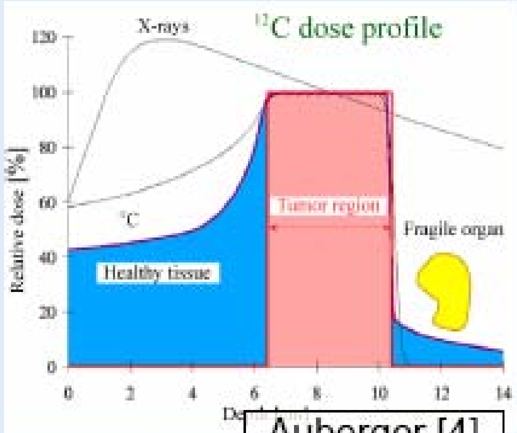
Carbon ion: presently, the best <u>high-LET</u> external radiation therapy

Protons vs ions

There are advantages and disadvantages to using protons or ions (nuclei or ions).

- Protons have almost no tail after the Bragg peak. (Once a proton has interacted it will generally not interact again. Ions contain other nucleons so they can interact again.)
- Ions have a sharper Bragg peak (lower overall dose for healthy tissue.)





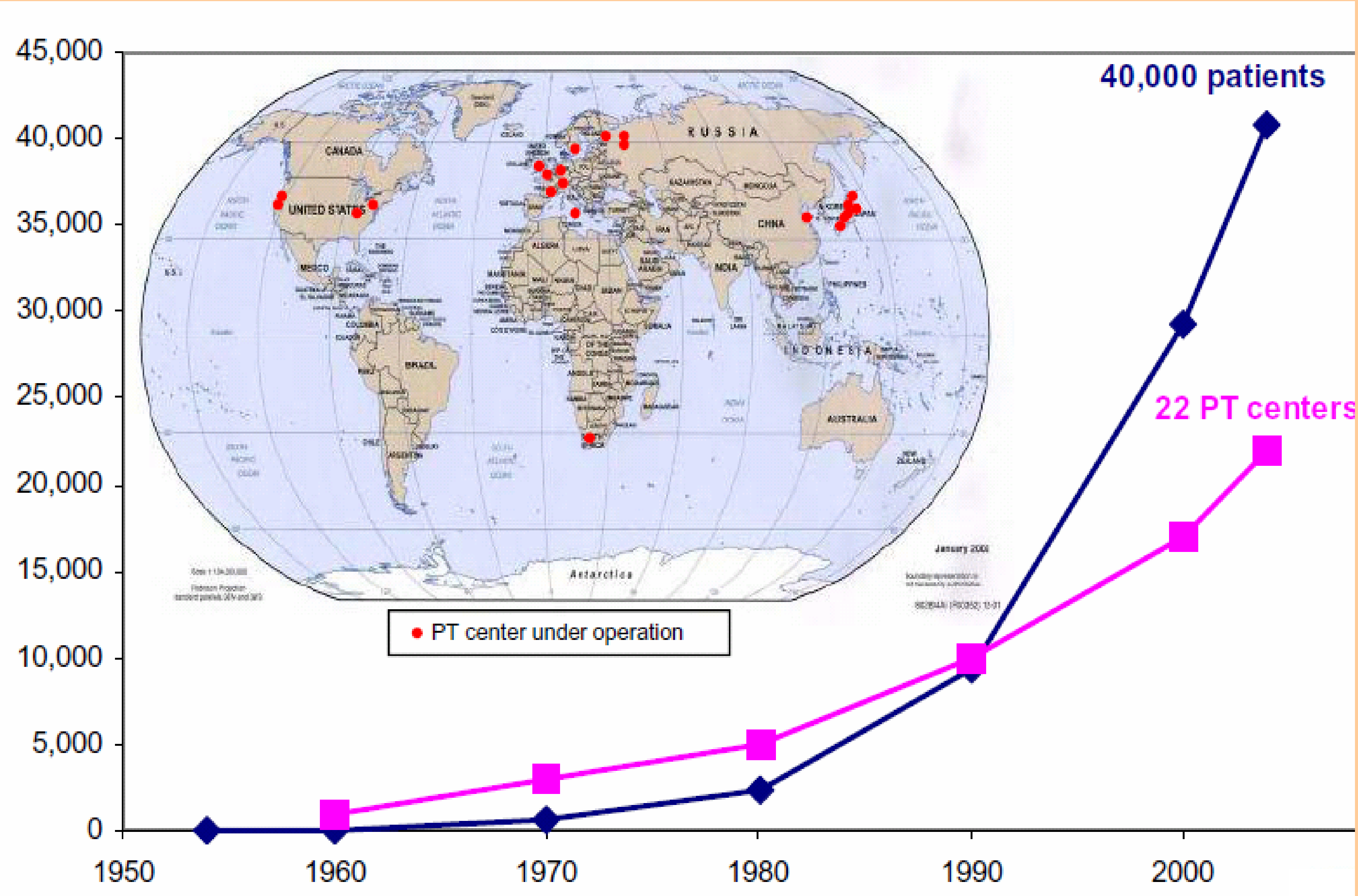
Auberger [4]

- Therefore we can use protons to treat a tumor close to a fragile and vital organ. (Such organs include eyes, the brain, the spinal column, the kidneys and the reproductive organs.)

Potential indications for carbon ion RT

- Skull base tumous
- Lung cancer
- Head and neck tumors
- Soft tissue sarcoma
- Pancreatic cancer
- Prostate cancer

Charged Particle Therapy [CPT] worldwide



Courtesy Janet Sisterson, MGH;
Presented by Ken Peach: Physics for Health, CERN, 2010.

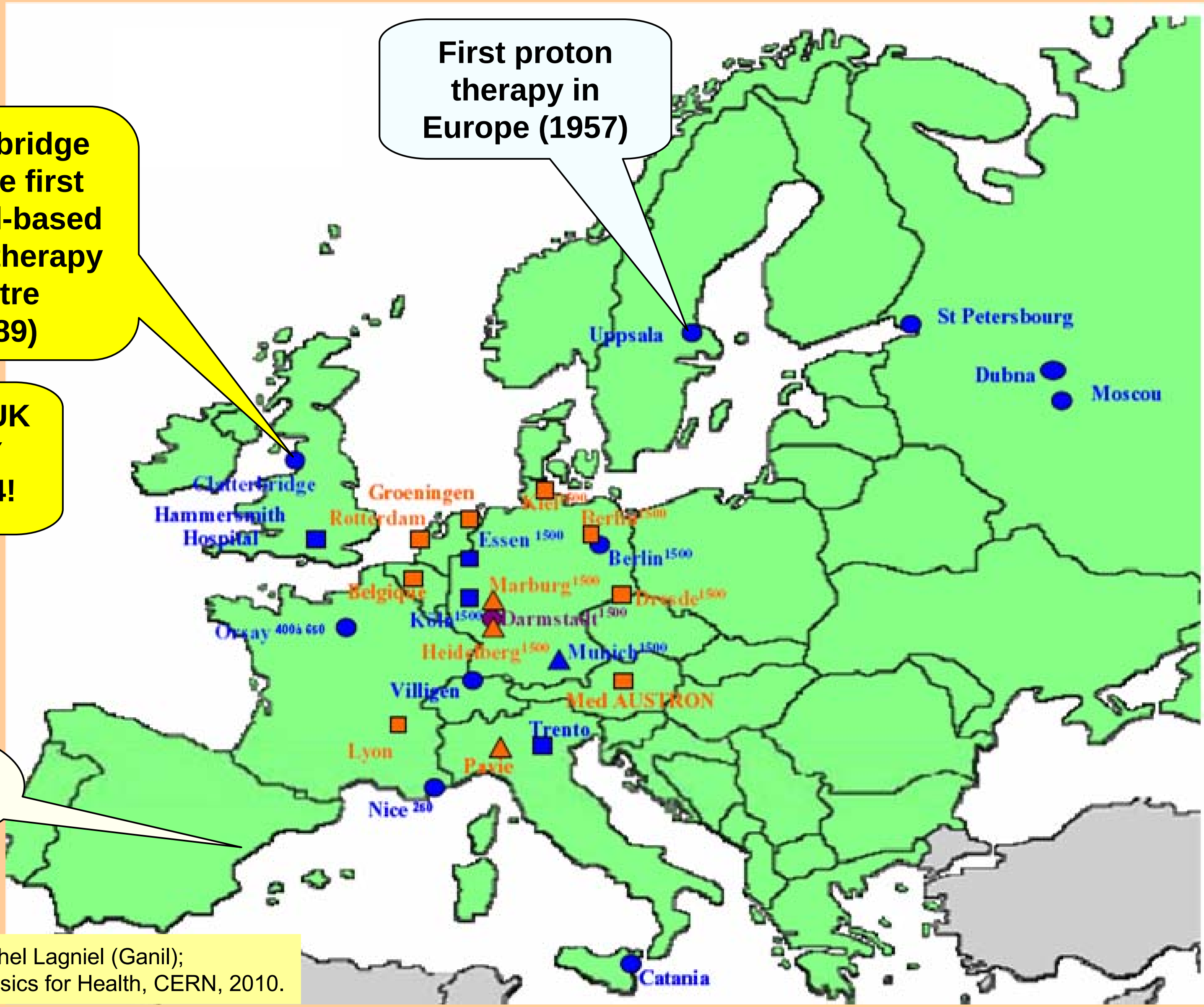
Charged Particle Therapy in Europe (existing and planned)

First proton therapy in Europe (1957)

Clatterbridge was the first hospital-based proton therapy centre (1989)

The second UK centre MAY open in 2014!

Plans for Valencia



Courtesy: Jean-Michel Lagniel (Ganil);
Presented by Ken Peach: Physics for Health, CERN, 2010.

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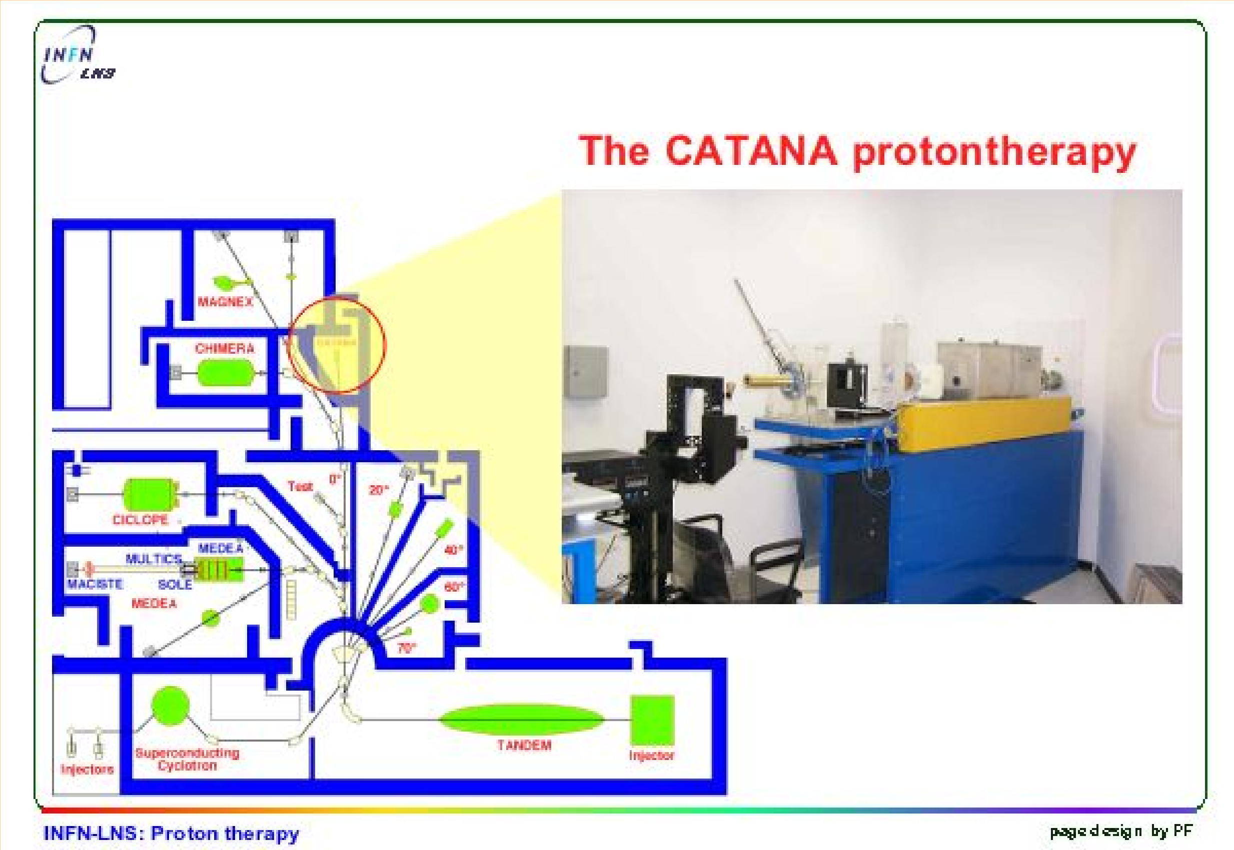

Activities of the Vinča – INFN/LNS group

Characterization of therapeutic beam at INFN-LNS

Provision of reliable experimental data for the validation and further development of the TPS (treatment planning system)

As the official members of the GEANT4 Collaboration at CERN (Geneva, Switzerland), work on the development of numerical radiobiological models to be used for evaluation of radiation induced damage

Heavy ion therapy

- **Radiobiological Research**
  - low dose effects
  - RBE (late effects, genetic mutation, transformation), prediction of radiosensitivity of different tumors and normal tissues, molecular correlates for radiosensitivity and RBE
  - chromosome damage
  - hypoxia
  - interaction of ion therapy and chemotherapeutic agents
  - integration of biologic data into biological modelling for treatment planning

Heavy ion therapy

- **Physics Research**
  - Clinical dosimetry for heavy ions is not at the same level of accuracy as dosimetry for conventional photon facilities (no primary standardization laboratory)
  - basic interactions of ions in the detector
  - accurate calculation of correction factors for ions (formation of a complex spectrum of secondary particles due to nuclear interactions = fragmentation spectrum)
  - Exploitation of Monte Carlo codes to study effects of fragmentation for dosimetry and treatment planning
  - working groups and technical partnerships

Heavy ion therapy

- **Clinical Research**
  - cross-disciplinary research (RB, clinicians, physicists), no stand-alone solutions for particle facilities, cooperation with universitary facilities necessary
  - clinical phase I-III trials on an international level to allow for sufficient patient numbers
  - further establishing clinical collaboration (multicenter trials)

Heavy ion therapy

- **Networking**
  - Transfer and exchange of experience and knowledge is essential in all subfields of heavy ion research
  - central study board (information about ongoing trials, contact persons, supporting and coordinating patient referral, protocol review, commissioning and monitoring of international trials
  - European Hadron Radiobiology Laboratory
  - IT solutions for data exchange
  - education / teaching of young scientists

The European Network for LIGht ion Hadron Therapy is a multidisciplinary platform that aims at a coordinated effort towards ion beam research in Europe.

The ENLIGHT network is formed by the European Hadron Therapy Community which consists of more than 150 researchers, belonging to more than fifty European Universities and research Institutes from sixteen European countries.