# Outline

# *Radiation to produce biological damage*

- Doses of the order of 1 Gy have to be provided
  - 1 Gy = 1 Joule / 1 Kg

- In which way the tissues have to absorb this amount of energy to obtain the desired result?

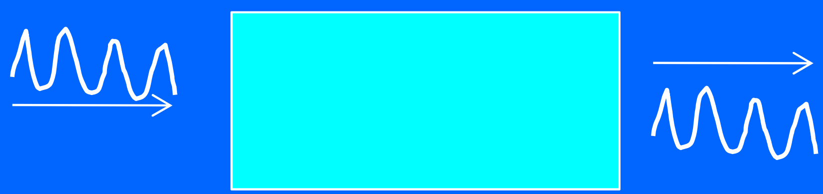
- Radiobiological damage deals with chemical bonds
  - Energies of the order of 10 eV
  - …but 1 J is one billion of billions larger! (1 eV = 1.6 E-19 J)

- We have to find good carriers of energy (i.e. particles) in order to distribute inside the target volume a very large number of "bits of energy" (of the order of 10 eV)

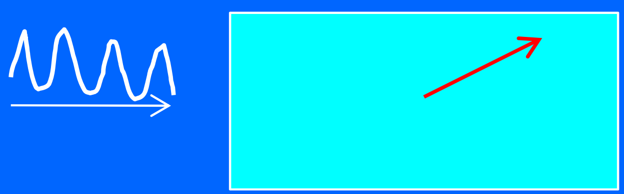
- This has to be done uniformly and sparing at best the surrounding volumes

# Photons

• **Single photon energy of the order of 10 MeV**



**No interaction, no energy is transferred**



**Interaction, charged particles (ex. electrons)**

**with energy of the order of 1 MeV are formed**

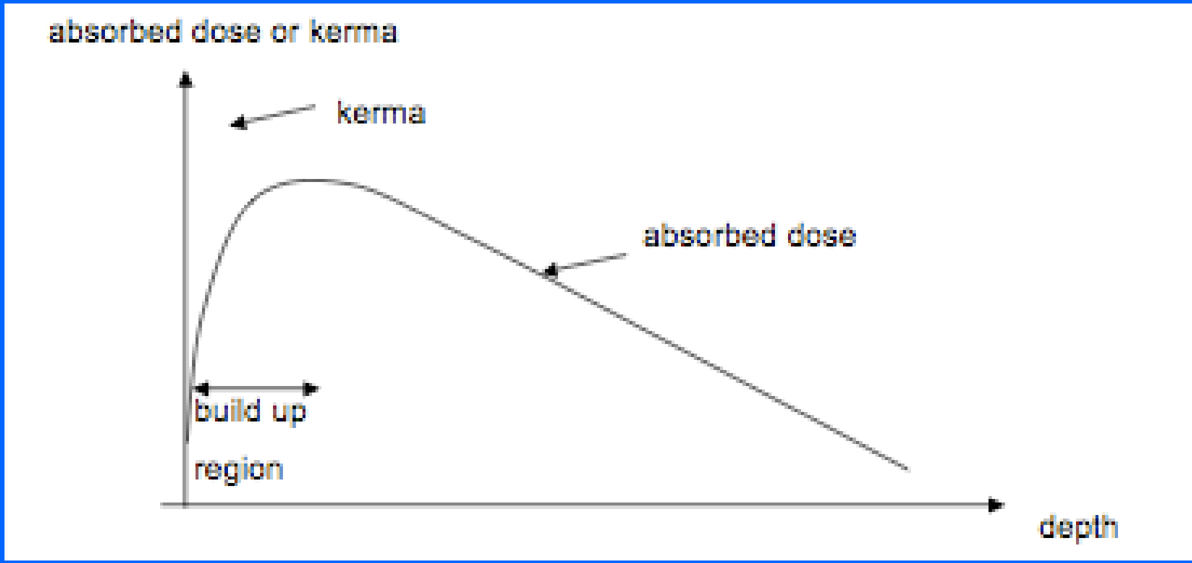
**These particles produce other interactions releasing energy "in 10 eV bits" (ionization, biological damage)**

**The process for a single photon is unpredictable.**

**Statistics governs these processes.**

# Photons

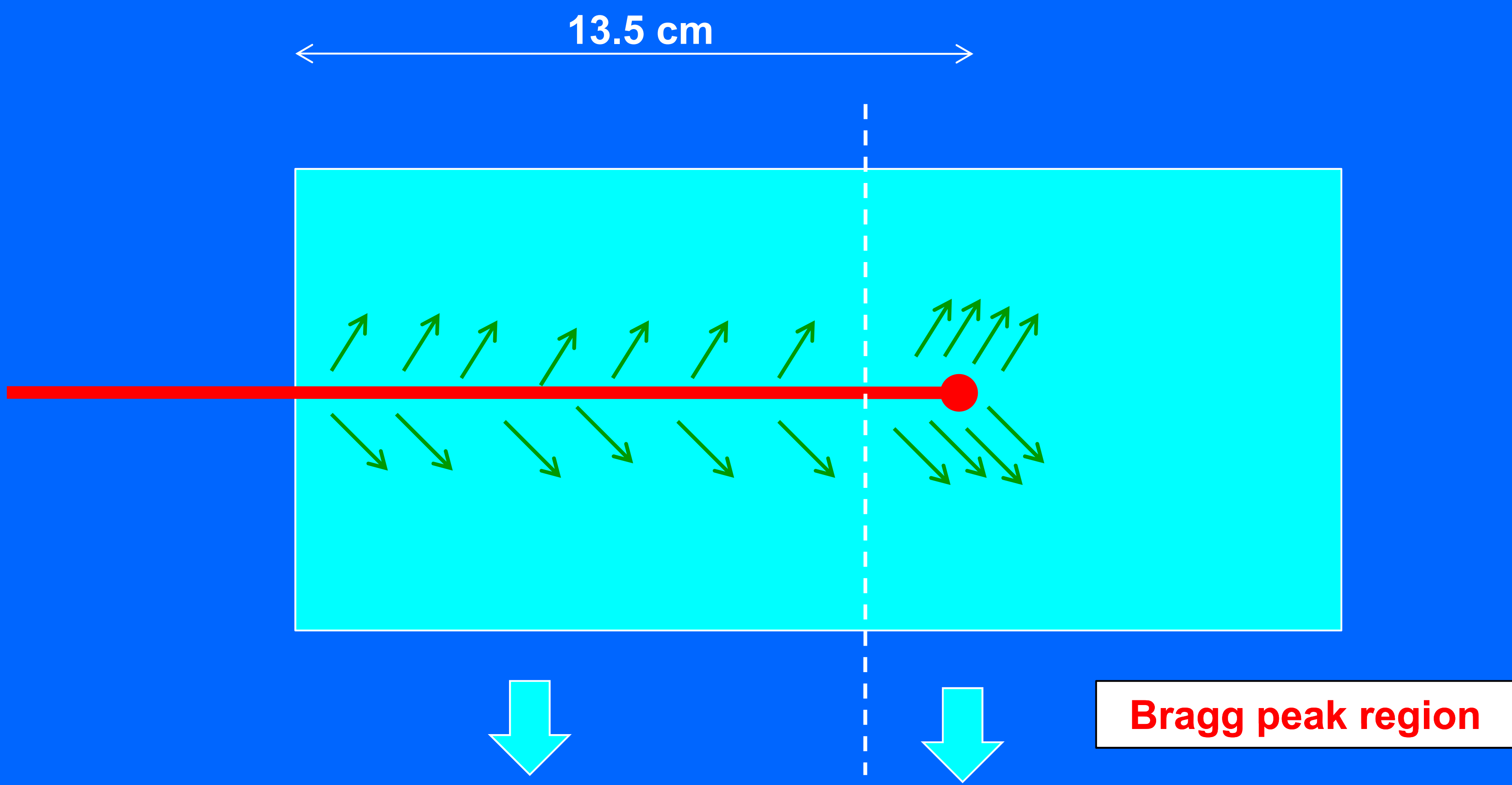
• Since thousends of billions of MeV photons are used in radiation therapy, the effects are deterministic and can be calculated




**About 20'000 patients per year every 10 million inhabitants are treated with photons produced by electron linacs**

# *And charged particles such as protons?*

- **Single proton, energy of the order of 140 MeV**




**The proton slows down, producing some interactions (ionization) releasing energy (about "10 eV bits")**

**The proton comes to rest, producing many interactions (ionization) releasing energy in 10 eV quantities (large biological damage!)**

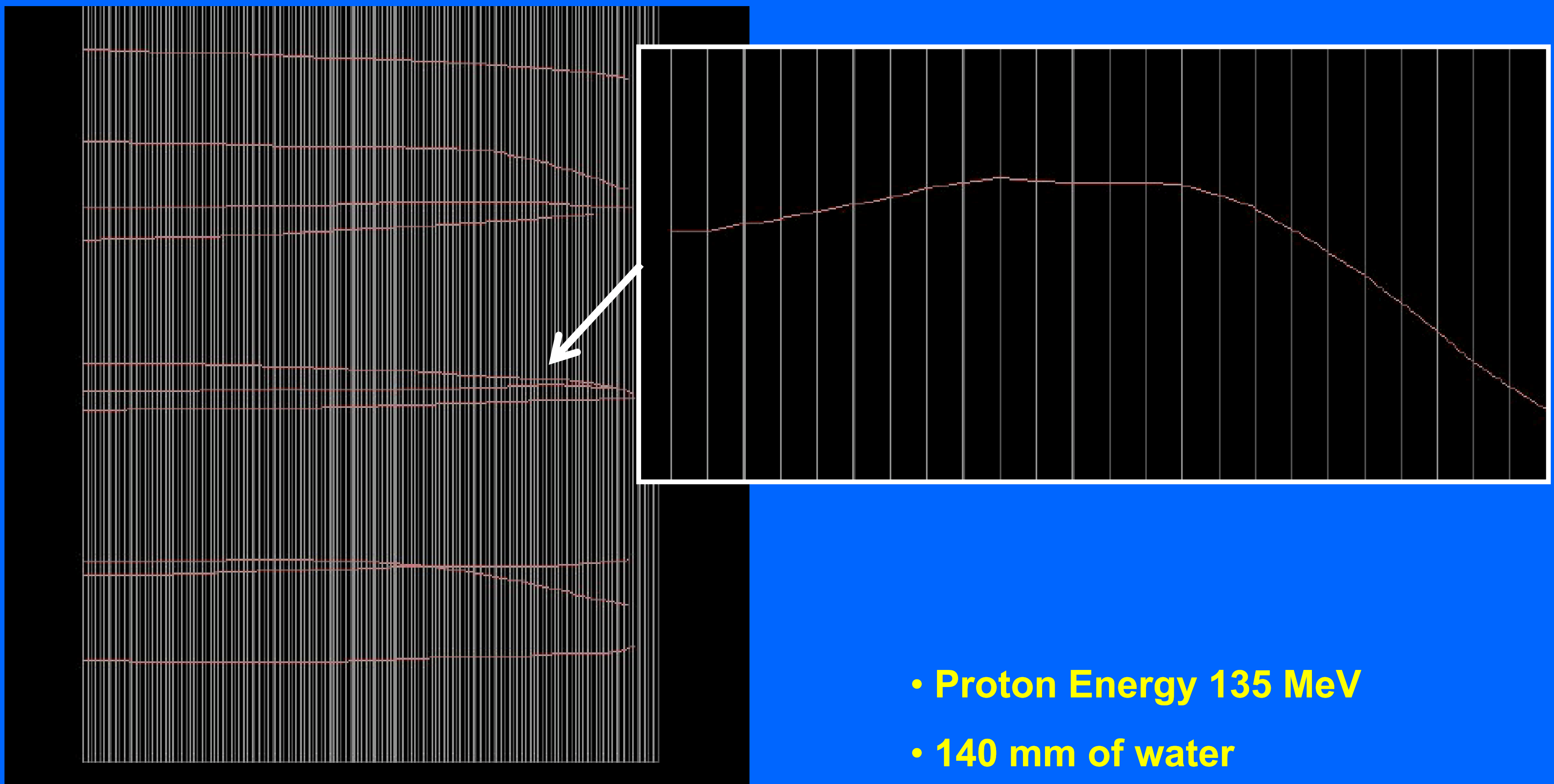
# *One important issue*

- **Protons and ions produce a Bragg peak and STOP! Fantastic but…**

- **…where?**
    - **Statistical processes determine the penetration and deviations from linear trajectory!**

- **Fortunately, billions of protons (ions) are used for therapy. The effects are deterministic and can be calculated!**

# *Simulation of protons in water*



S. Studer, LHEP, UniBe

- **Proton Energy 135 MeV**
- **140 mm of water**
- **Each "slice" is 1 mm**

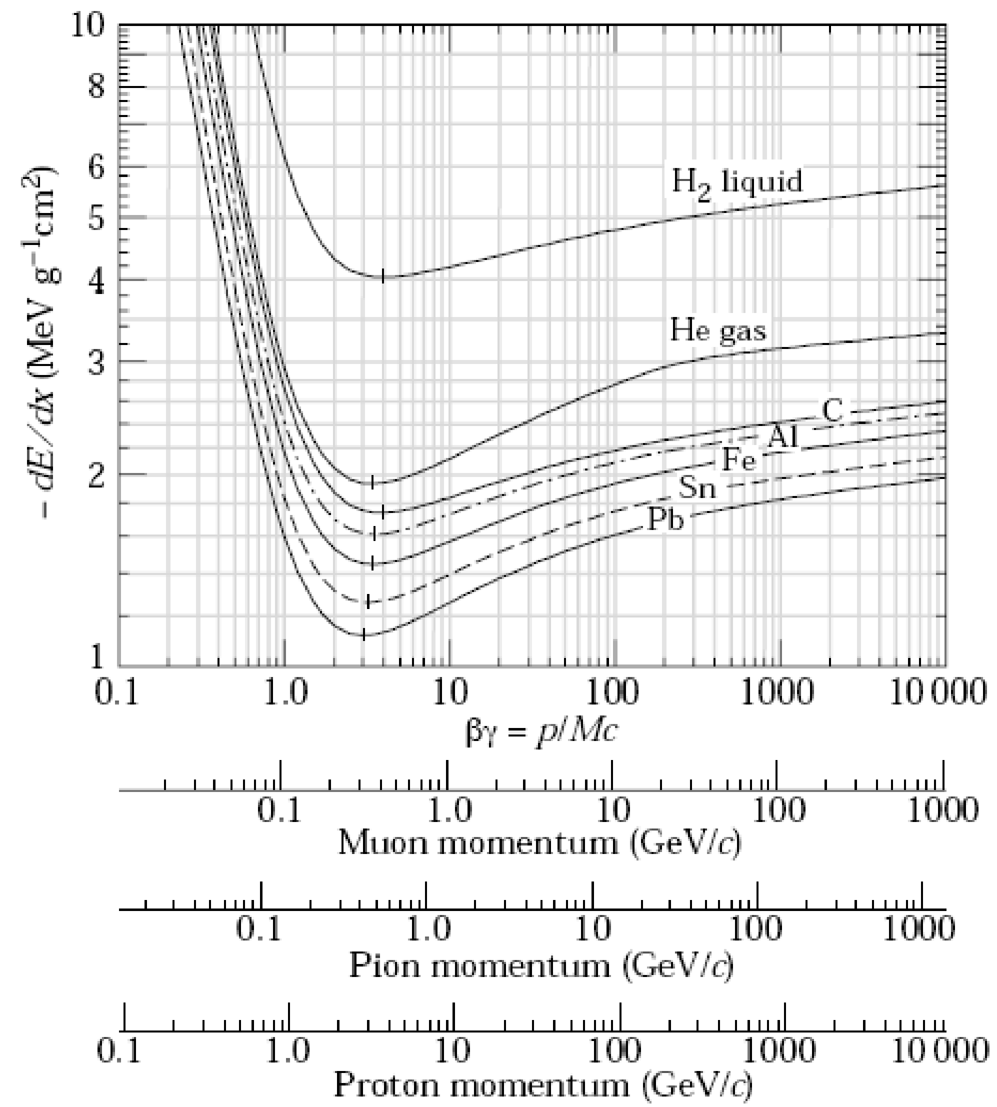
**The Bethe-Bloch formula:**

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

$$K = 4\pi N_A r_e^2 m_e c^2/A$$

**= 0.3071 MeV / (g/cm²)**

**dx expressed in g/cm²**



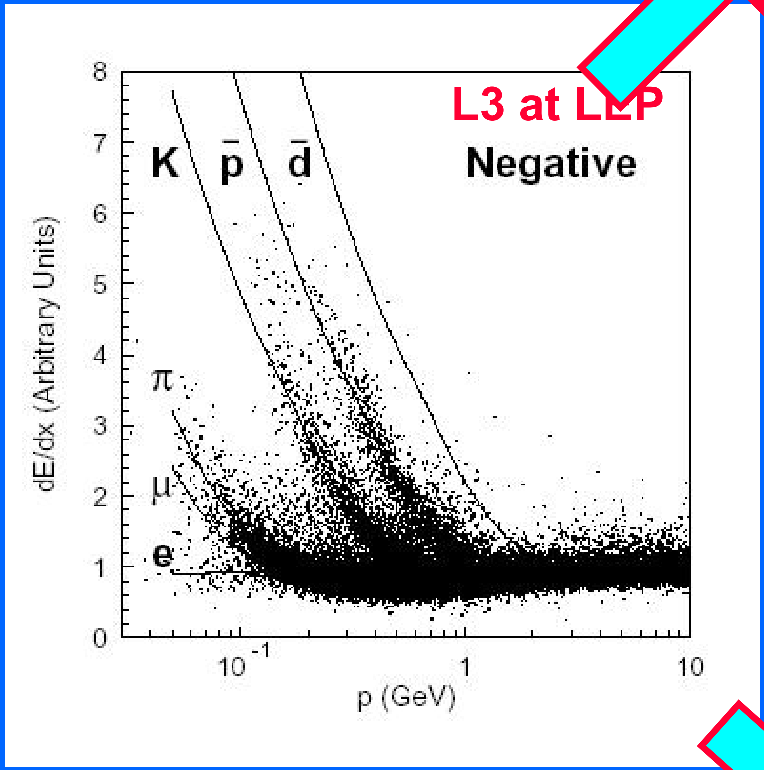

**Notes:**

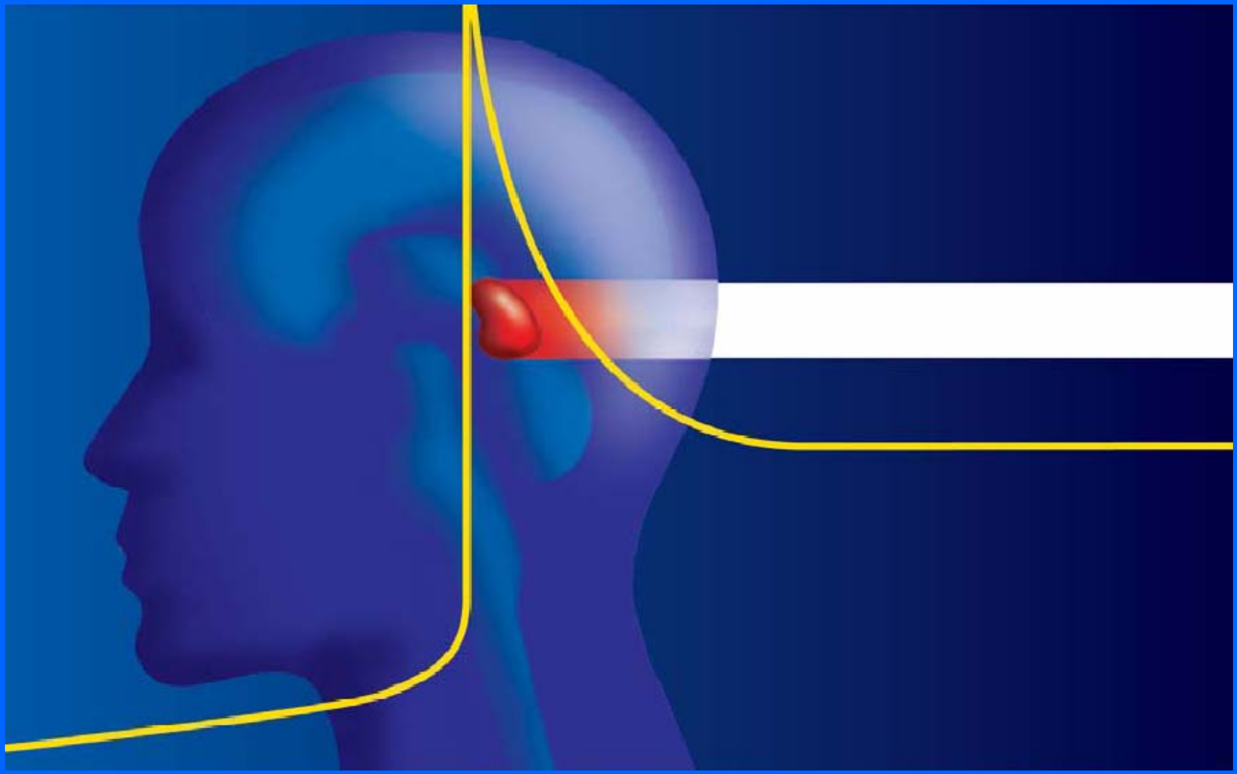
- **Ionization + eccitation**
- **MIP = Minimum Ionizing Particle**
- **MIP in water 2.0 MeV/cm → 0.2 eV/nm very low LET radiation !**

# *The basic concept of hadrontherapy*

**Fundamental physics**

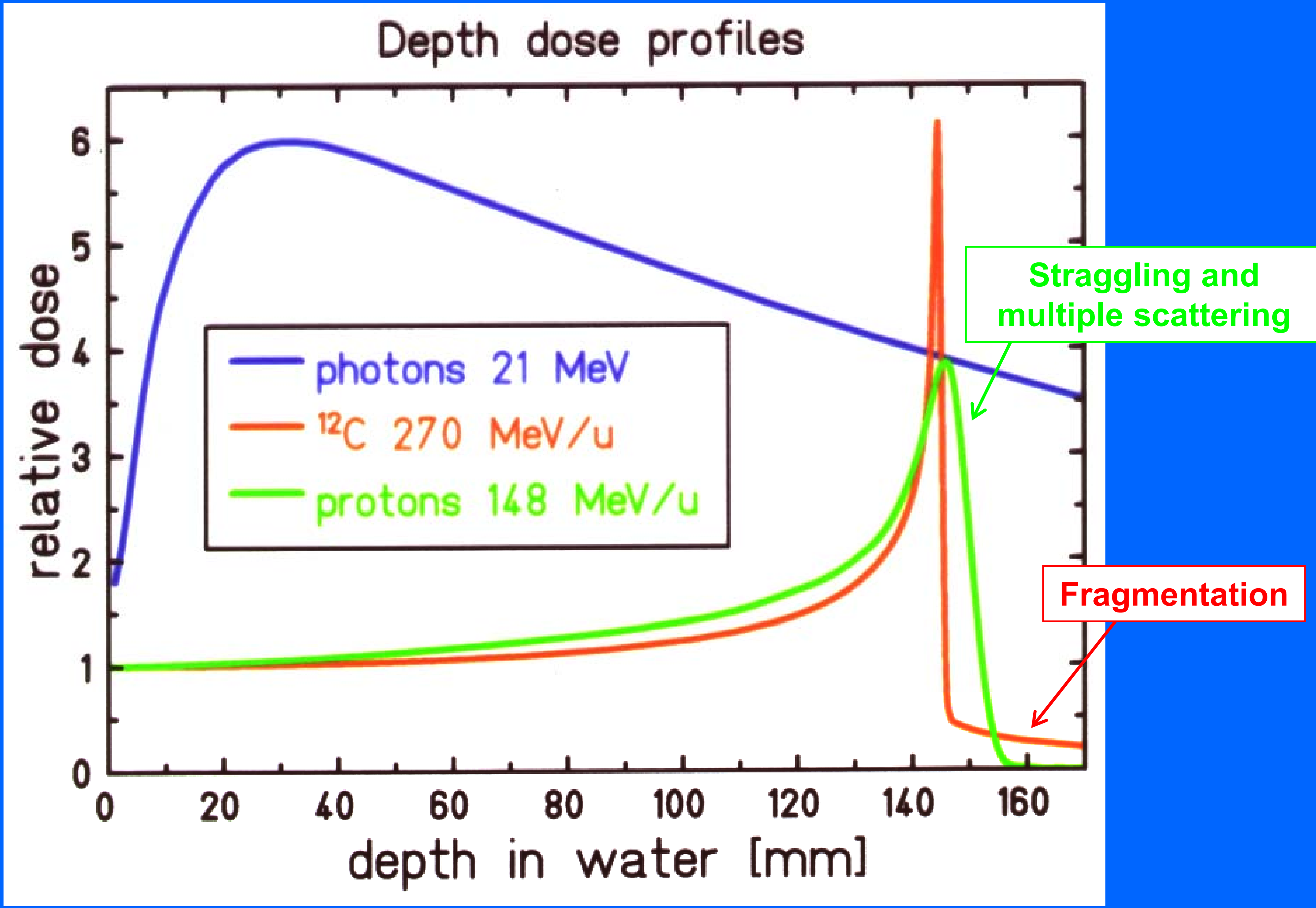
**Particle identification**



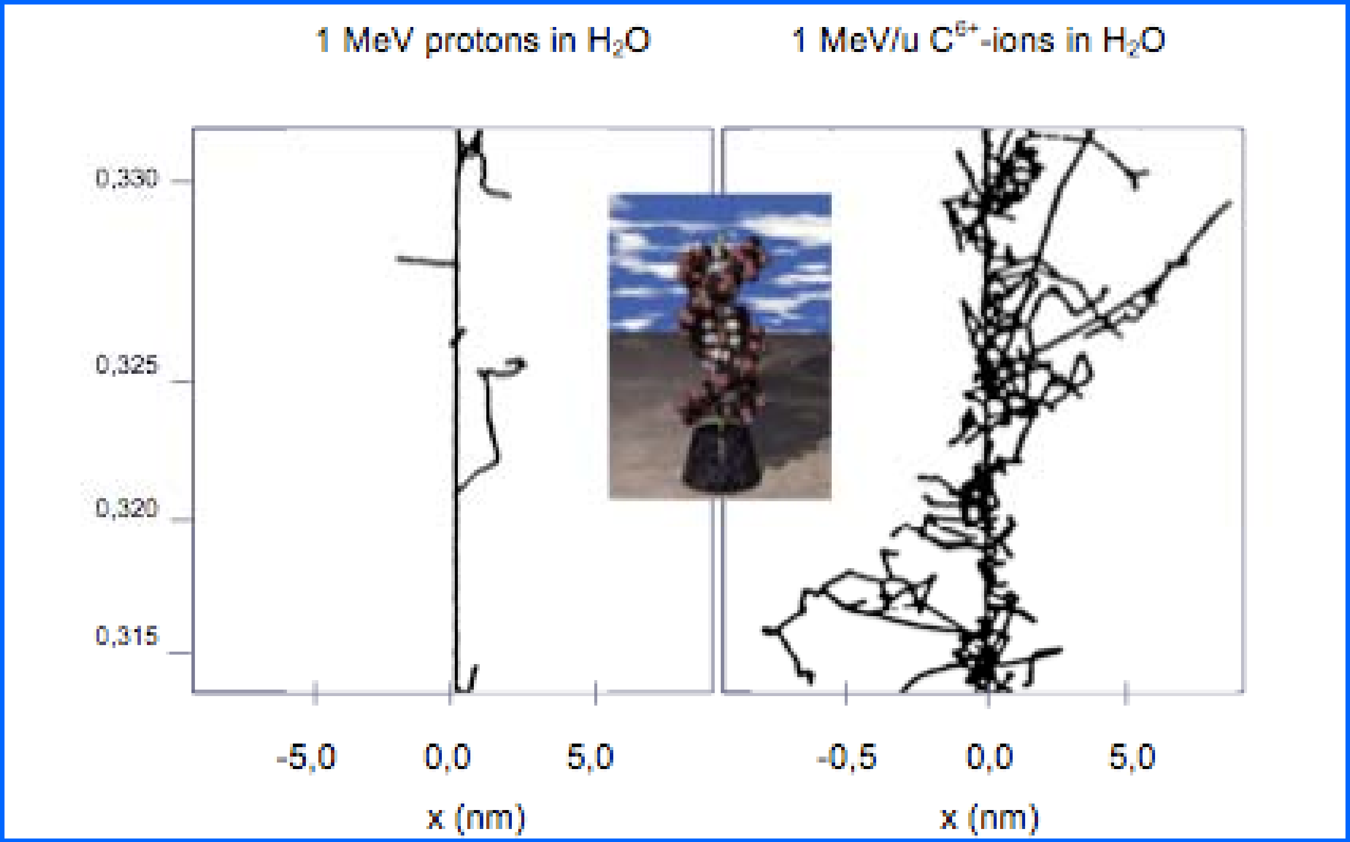



**Medical applications**

**Cancer hadrontherapy**


Depth dose profiles
relative dose
depth in water [mm]
0
1
2
3
4
5
6
0
20
40
60
80
100
120
140
160
photons 21 MeV
12C 270 MeV/u
protons 148 MeV/u
Straggling and multiple scattering
Fragmentation

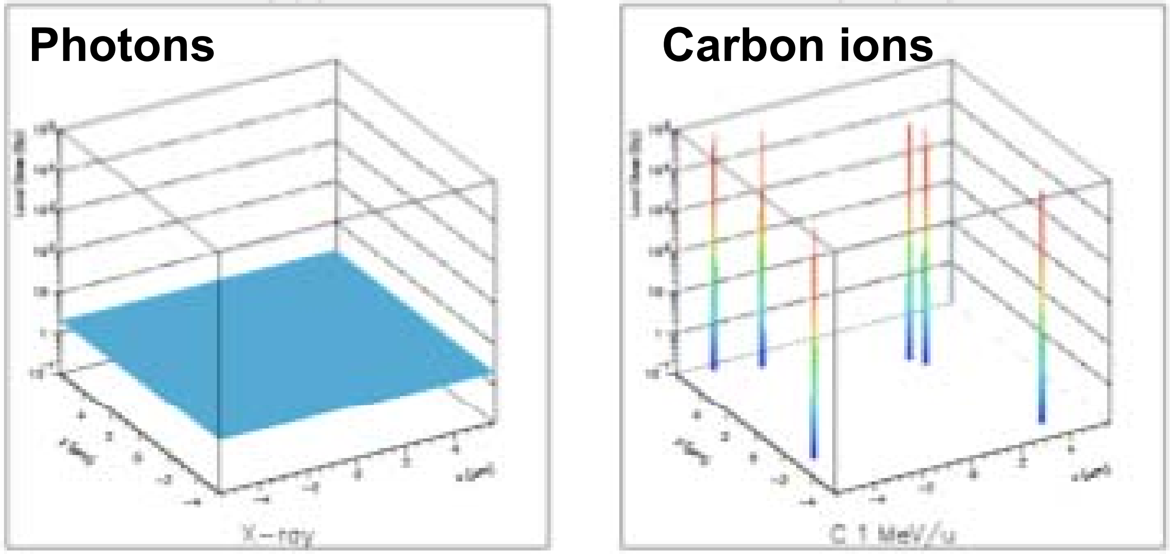
# *Ionization at nanometric scale*




Courtesy GSI

**Low LET** **High LET**

# Calculations and experiments




**Simulation on a nucleus of a cell**

**(about 10 um x 10 um)**

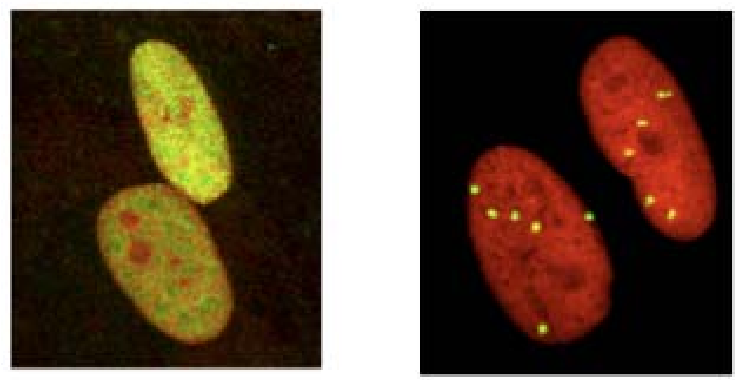
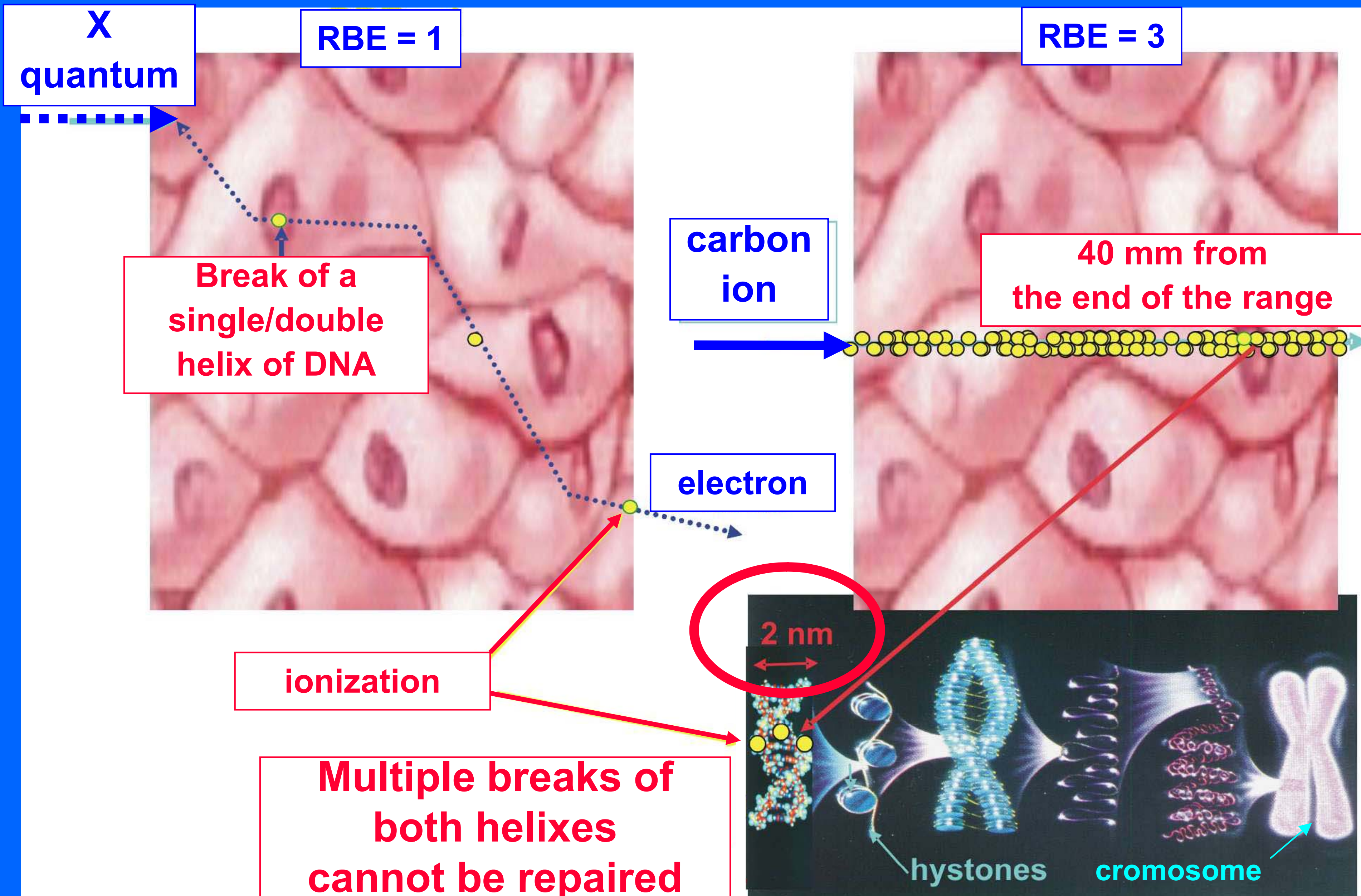


Fig. 9: left: photons deposit their energy randomly distributed and thus nearly homogeneously over the irradiated medium; right: ions transfer their energy to the liberated electrons, which form a track around the particle trajectory. In a high LET track the damage is produced in high density and thus with a high possibility to form "clustered lesions" which are to a large amount irreparable. The immunofluorescence-stained visualisation has been described by [32].

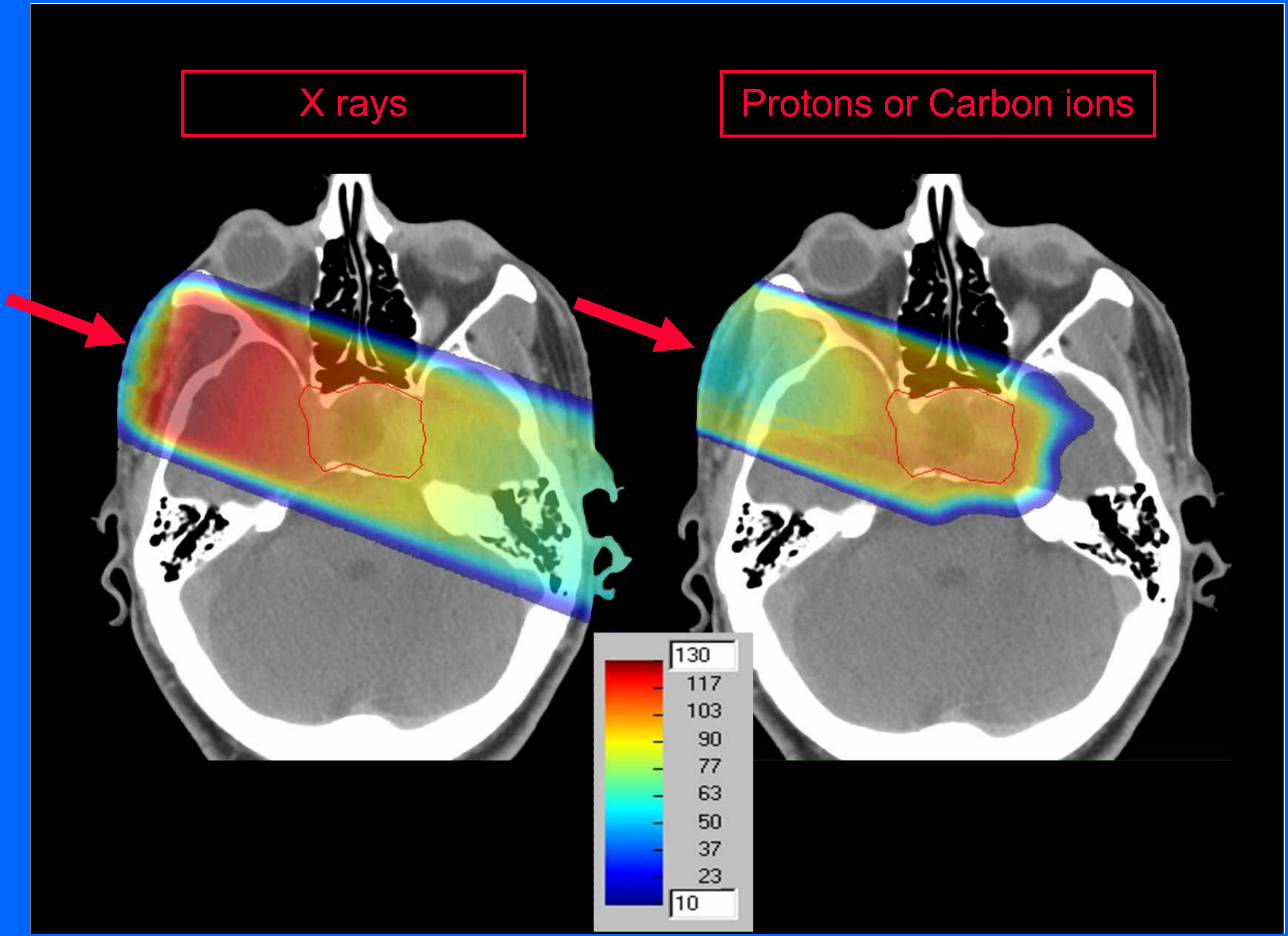
Courtesy GSI

# *Why ions have a large biological effectiveness?*




Multiple breaks of both helixes cannot be repaired

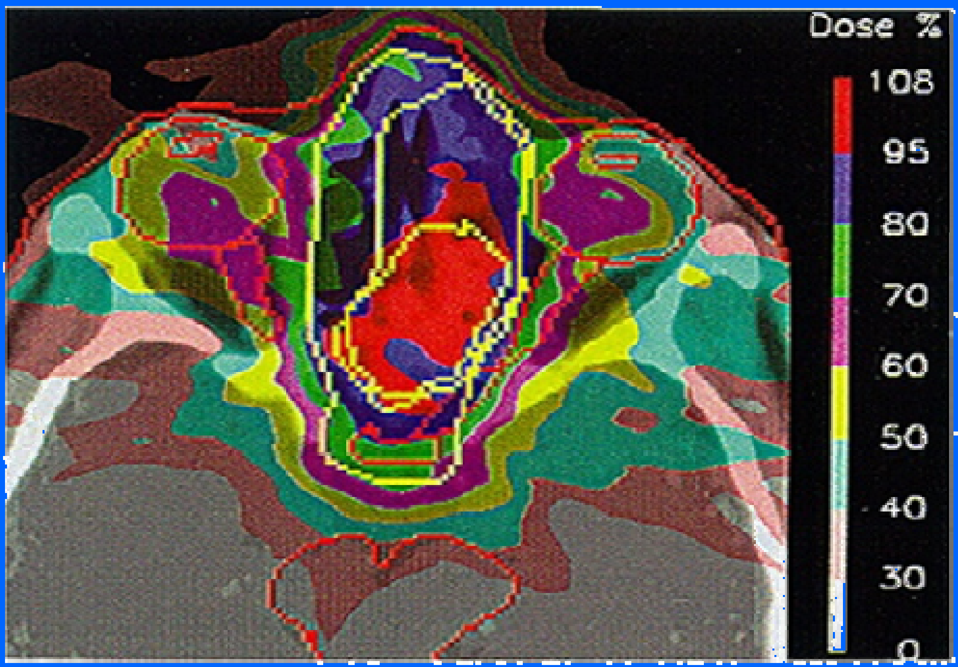
# Single beam comparison



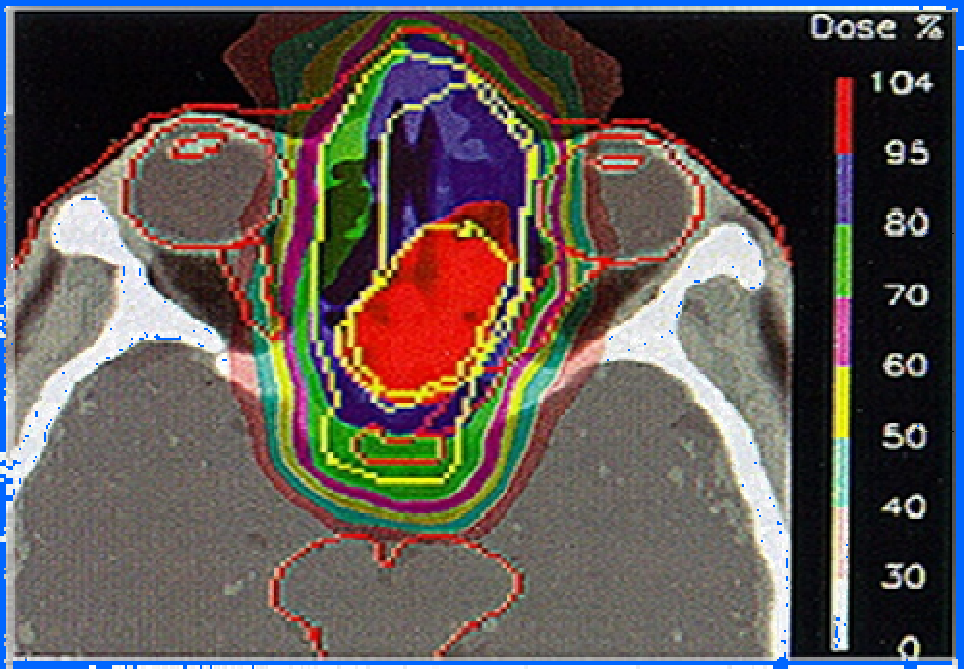
# *Protons and ions are more precise than X-rays*

**Tumour between the eyes**

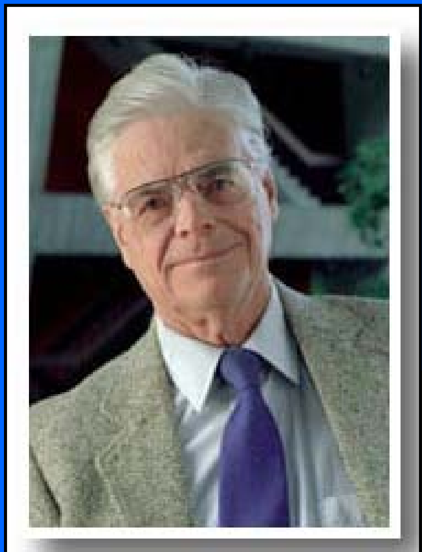
**9 X ray beams**




**1 proton beam**



# *The first idea – Bob Wilson, 1946*



- Bob Wilson was student of Lawrence in Berkley
- Study of the shielding for the new cyclotron
- Interdisciplinary environment = new ideas!
- Use of protons and charged hadrons to better distribute the dose of radiation in cancer therapy

# A very interesting and still actual paper!

## 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, and alpha particles from present accelerators. Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 Mev (million electron volts) and perhaps as high as 400 Mev. The range of a 125 Mev proton in tissue is 12 cm., while that of a 200 Mev proton is 27 cm. It is clear that such protons can penetrate to any part of the body.

The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. The dosage is proportional to the ionization 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 collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible.

Let us examine the properties of fast protons somewhat more quantitatively. Perhaps the most important biological quantity is the specific ionization, or number of ions per centimeter of track. This quantity is not difficult to calculate. The results of such calculations are shown in Figure 1, where the range of protons in tissue is plotted for protons of various energies. In the same figure, the specific ionization is plotted as a function of the range in tissue. For purposes of calculation, tissue has been assumed to have the molecular formula (1): $C_{5.5}H_{40}O_{3.1}N_{0.15}$, and to be of unit density, *i.e.*, 15 per cent protein and 85 per cent water. The calculations can be easily extended to other materials and densities.[2] The accuracy is perhaps 5 per cent. However, exact values for various tissues can be quickly measured as soon as the fast protons are available.

Figure 1 shows, for example, that if we want to expose a region located 10 cm. be-

[1] Accepted for publication in July 1946.

[2] The range of a proton in air in meters is given by the convenient formula $R = (E/9.3)^{1.8}$ where the energy is expressed in Mev. The range in tissue is $1.11 \times 10^{-3}$ times the range in air. The stopping power of other substances may be found in Livingston and Bethe: Rev. Mod. Physics 9: 245, 1937. The physical calculations of this paper will be submitted to the *Physical Review* for publication.



**R.R. Wilson, Radiology, 47 (1946) 487**

## *The beginning of hadrontherpay 1954 at Berkeley*

- 1948- Biology experiments using protons
- 1954- Human exposure to accelerated protons and alphas
- 1956 - 1986: Clinical Trials– 1500 patients treated

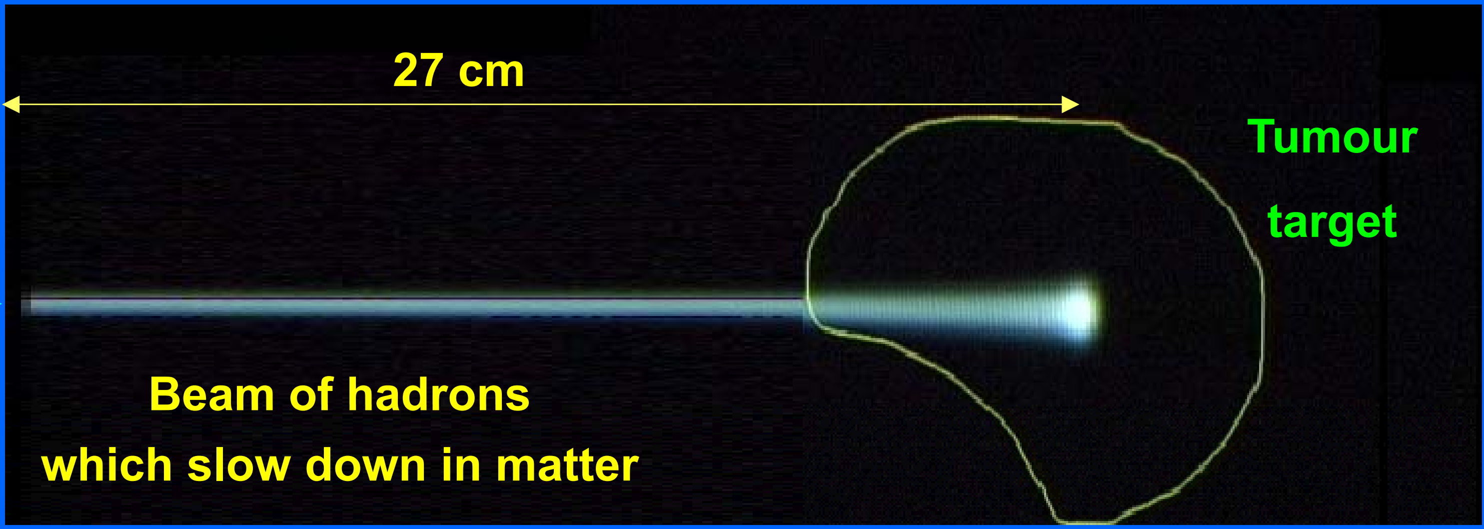
Cornelius A. Tobias

**C.A. Tobias, J.H. Lawrence et al., Cancer Research 18 (1958) 121**

# *The basic figures of hadrontherapy*

**Protons**
**200 MeV**
**1 nA**

**Carbon ions**
**4800 MeV**
**0.1 nA**




- Bragg peak
  - Better conformity of the dose to the target → healthy tissue sparing
- Hadrons are charged
  - Beam scanning for dose distribution
- Heavy ions
  - Higher biological effectiveness

- Why 200 MeV protons and 400 MeV/u C ions?
  - Range in water: 200 MeV p → 27 cm penetration depth
  - 4800 MeV C ions → 27 cm penetration depth

- Why 1 nA current?
  - Requirement: 2 Gy per Kg per minute
  - (2 J / 200 MeV) x (e) x (1/60 sec) ≈ 1 nA

## *Exercise: calculation of range, straggling and scattering with different materials and configurations using SRIM (www.srim.org)*

## *End of part V*