Nuclear Physics in Oncology: Hadrontherapy, BNCT and Flash therapy

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Outline

- Hadrontherapy what is it ?
  - Tumor control and cures
- Radiation in biological tissues
- Radiotherapy vs Hadrontherapy
- Ion beam in matter
- Nuclear effects in hadrontherapies
- Boron Neutron Caption Therapy
- Flash effect
- Summary

Tumours around the world

- About 3 ‰ of population will be diagnosed a **new** cancer each year

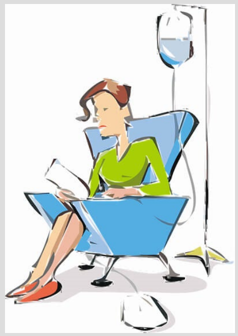
→19.3 million people/year

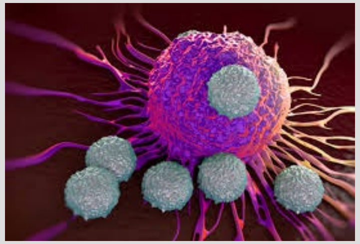
- The increase in lifetime will make this number even worse!

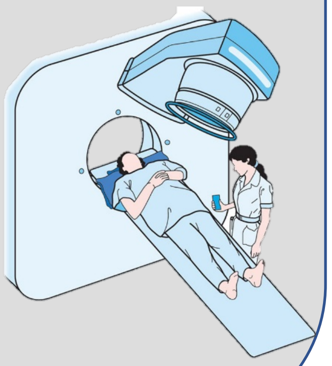
(28.4 M/year by 2040)

- No surgery on elderly patients!

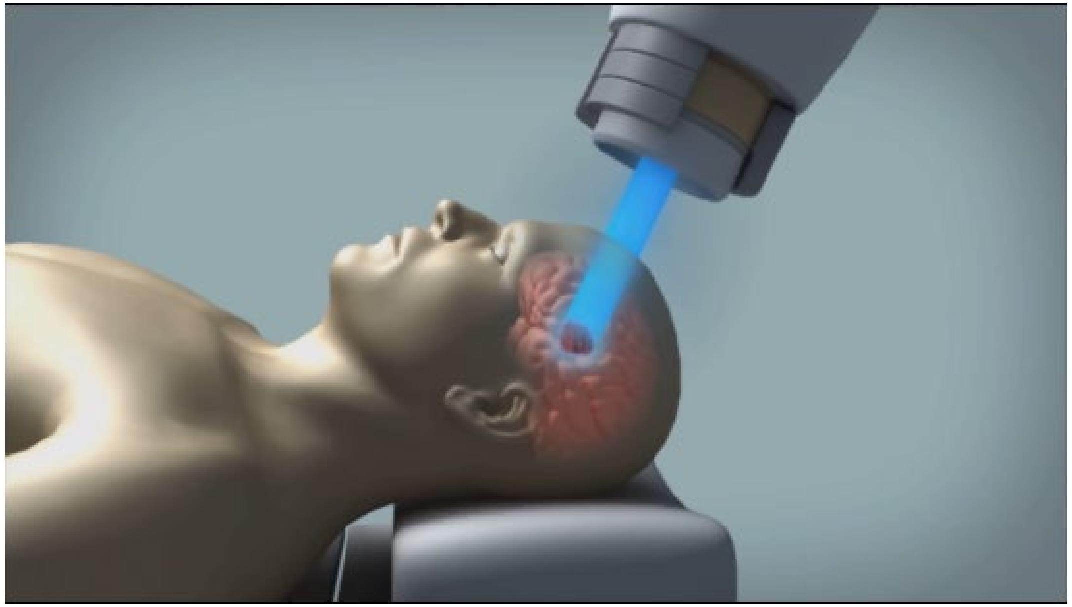
- ❑ **Surgery**
- ❑ **Chemiotherapy**
- ❑ **Immunotherapy**
- ❑ **Radiotherapy**
- ❑ **Hadrotherapy**







What is hadron therapy ? A treatment with particle beams!

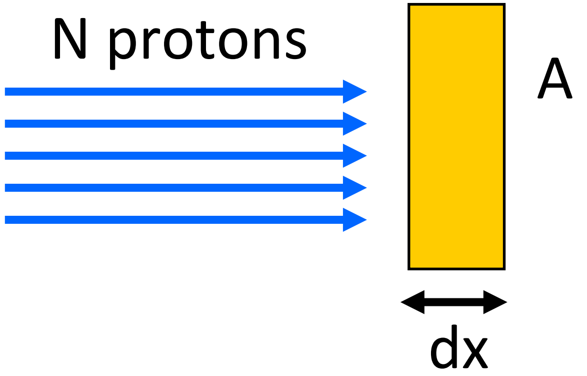


- Typical application:
  - Solid tumor
  - Otherwise healthy patient
- Beam of charged particles
  - Protons, ^{12}C (but also ^{4}He, ^{16}O)
  - → Accelerator
- Advantages:
  - Better efficacy
  - Spare healthy tissues
  - Lower collateral effects
- Disadvantages:
  - Higher costs
    (ITA: 21 k€ hadro vs 12 k€ radio)
  - Less treatment centers

Dosimetric quantities

Fluence $\Phi = \frac{dN}{dA}$ (Ions/cm^2)

- dN: Number of particles (ad ex. protons in a beam)
- dA: Infinitesimal area ⊥ to the beam



Flux $\dot{\Phi} = \frac{d\Phi}{dt}$ (Ions/cm^{2}s)

Dose $D = \frac{dE}{dm}$

absorbed energy dE (given by radiation) per mass unit dm (it does not take into account the biological effects)

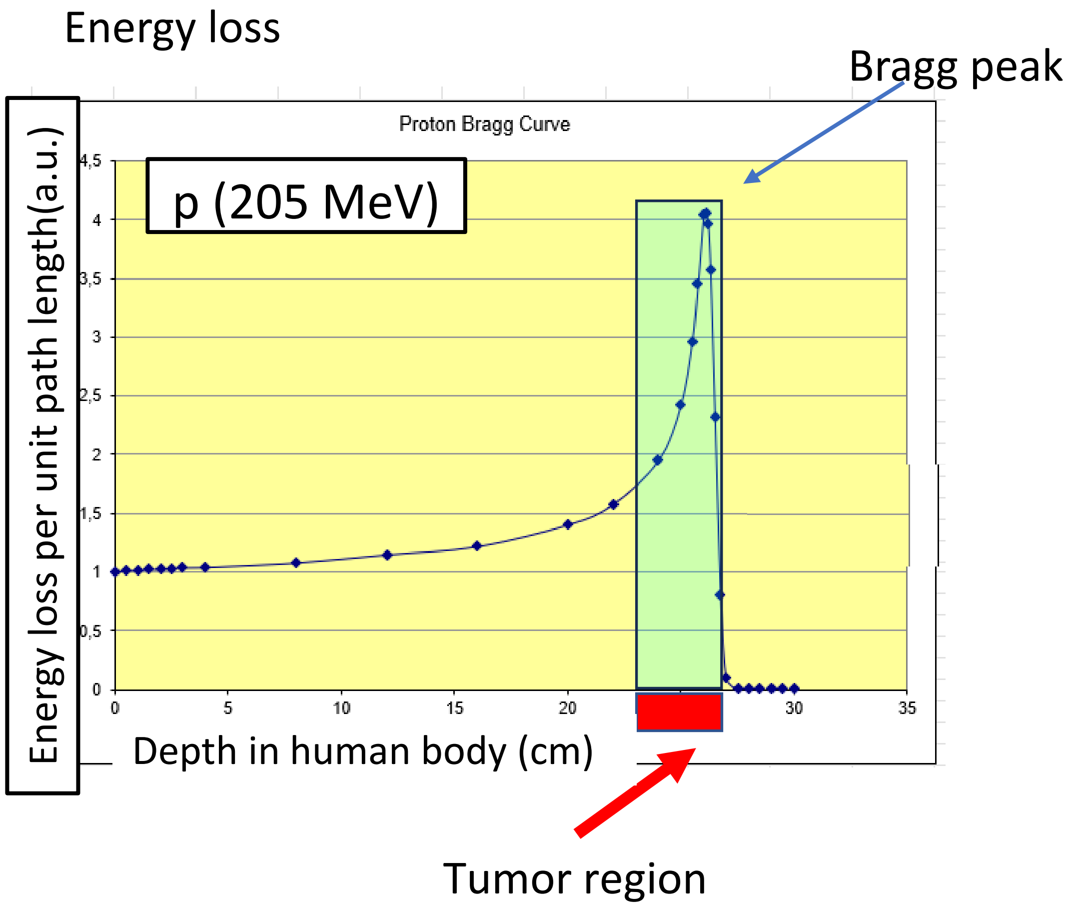
In SI the unit is **Gray** = 1 J kg^{-1}

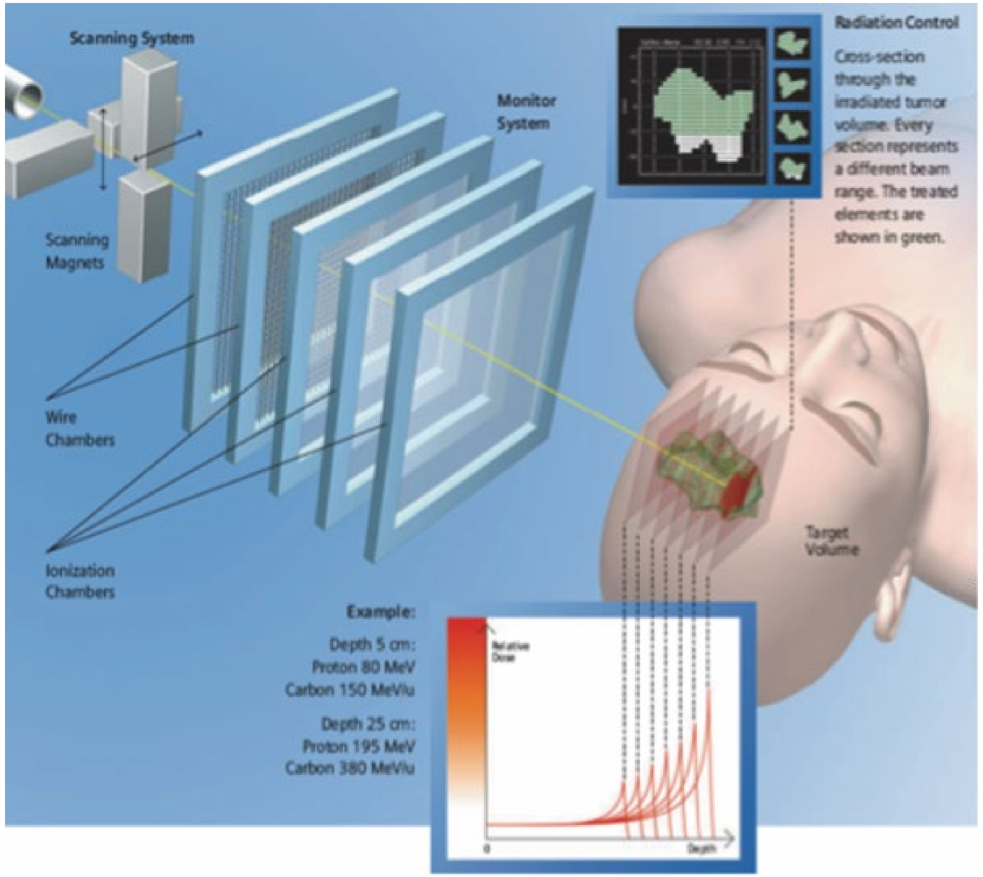
Dose equivalent (Sievert)

$$H = D \times W_R \times W_T$$

Radiation type	w_R
X and γ rays	1
Electrons and muons	1
Protons and charged pions	2
α particles and heavy ions	20
Neutrons	2–20
Organ	w_T
Breast, bone marrow, lung, colon, stomach	0.12
Gonads	0.08
Bladder, liver, esophagus, thyroid	0.04
Bone surface, brain, salivary glands, skin	0.01
Remainder	0.12

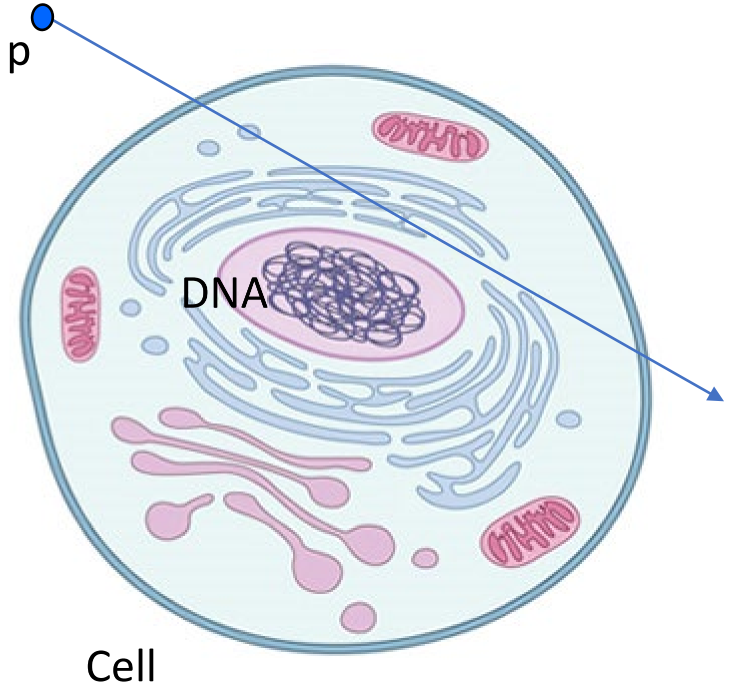
How it works?



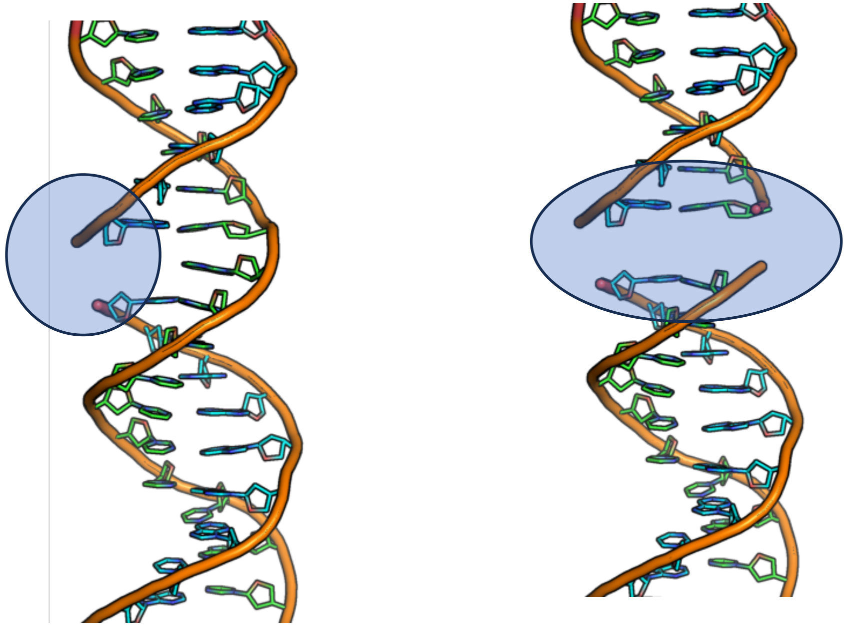


The position of the bragg peak is controlled by the beam energy
Changing x,y and energy you can span on all the tumor volume
Accuracy: order of mm

Radiation biology



An ion traveling in matter releases charges
Charges will produce a release of $OH^{\bullet}$ free radicals in the cell
$OH^{\bullet}$ free radicals might attach and damage the DNA

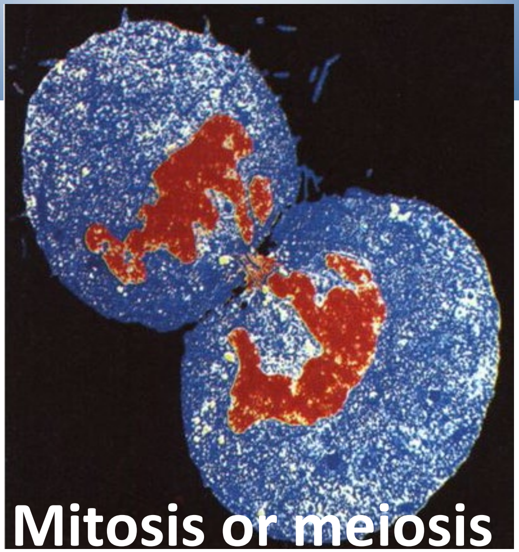


Single strand break
→ reparable!

Double strand break
→ NOT reparable!

Cell is still alive;
Limited problems on cell metabolism

Effects of a damaged DNA chain

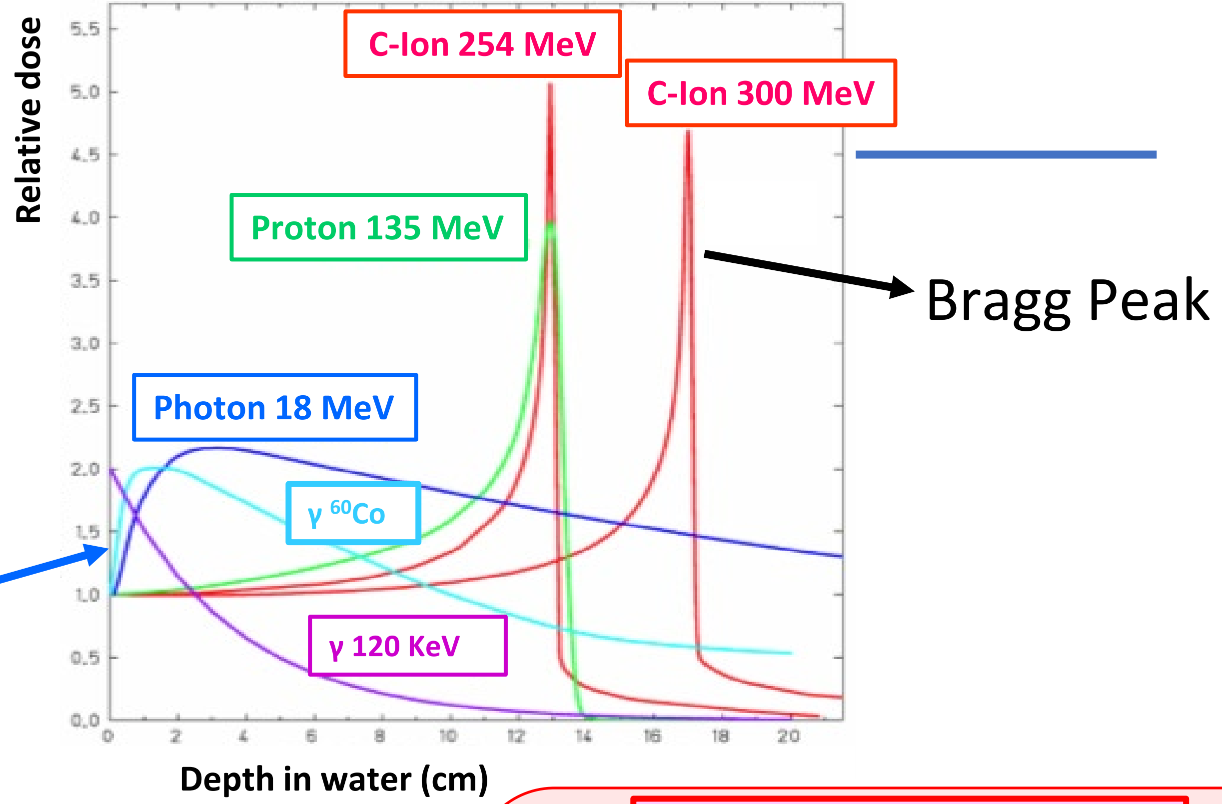


Cancer is a **mutated cell** that has lost control of its reproduction. It proliferates in a disorded way.

to prevent the indefinite proliferation not necessary to kill the cell

- **Hit the DNA, damaging it the hard way**
- **Cells looses the capability to reproduce**
- **At mitosism the cell goes towards apoptosis**
- **Result: tumor reduction vs time**

Hadrontherapy vs Radiotherapy

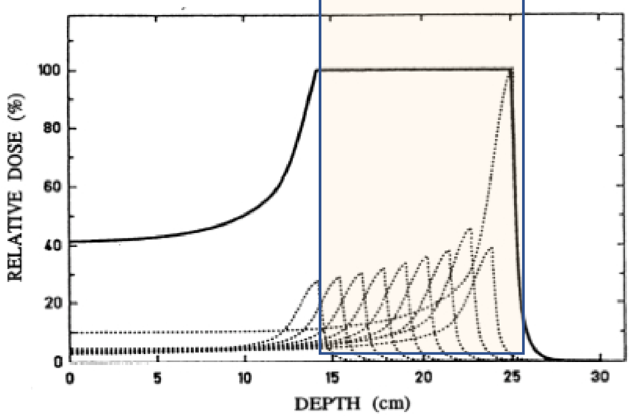


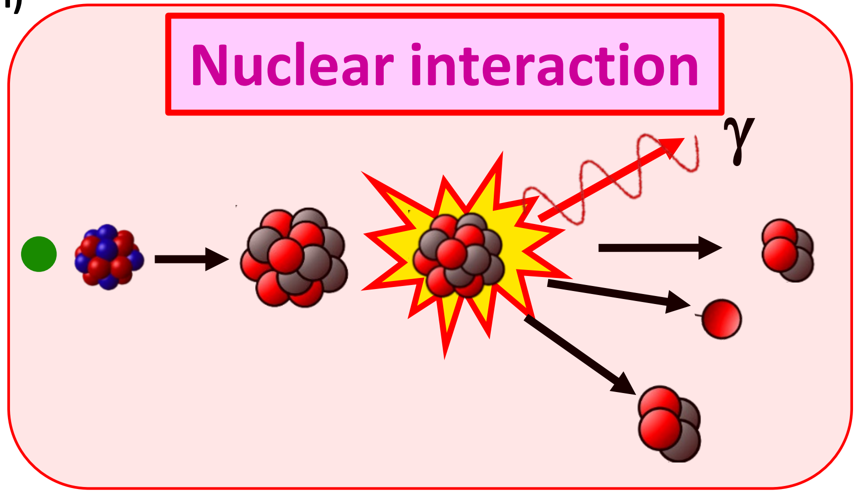
Gamma

- Photoelectric
- Compton
- Pair production

Pros and contra

- **Better dose profile from hadrons**
- **Penetration depends on energy**
- **MORE expensive than γ**
- **Nuclear effect not completely known**





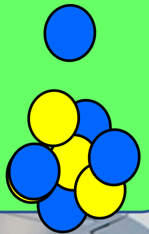
Radio- vs Hadron- therapy

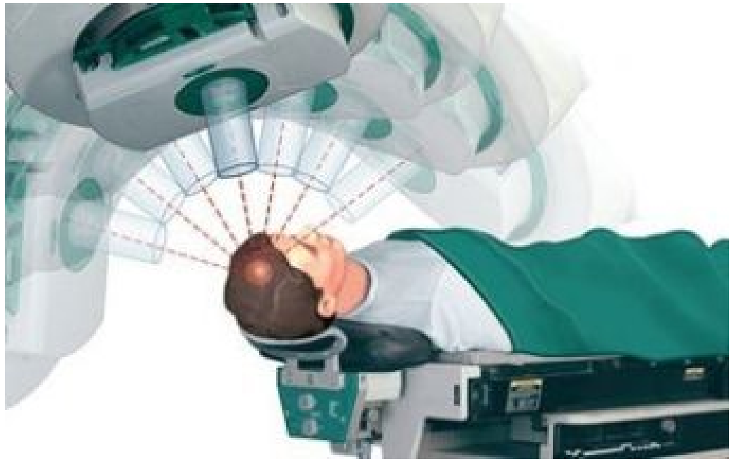
Radiotherapy

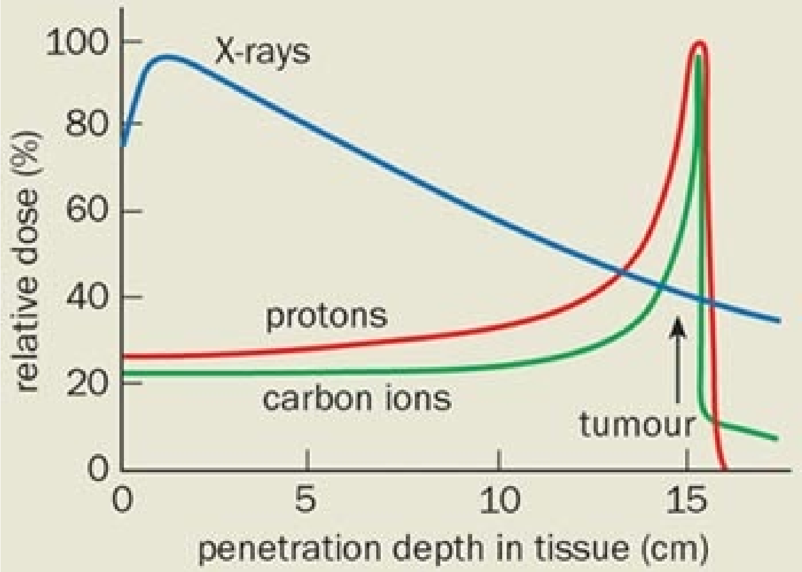
Hadrotherapy

p

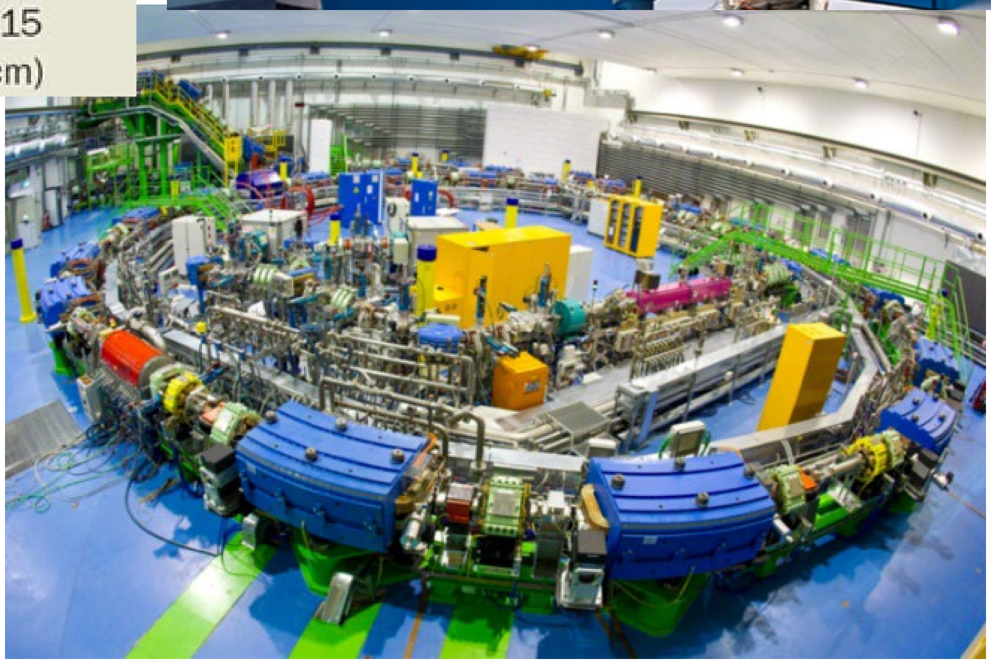
^{12}C



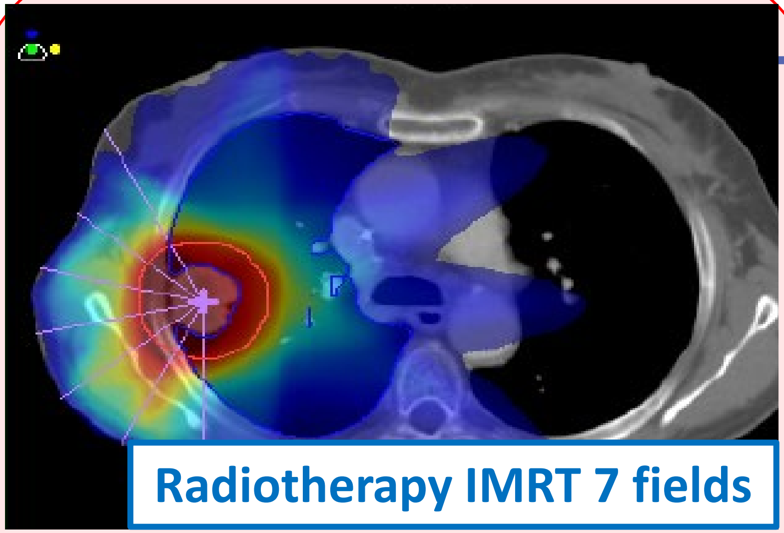


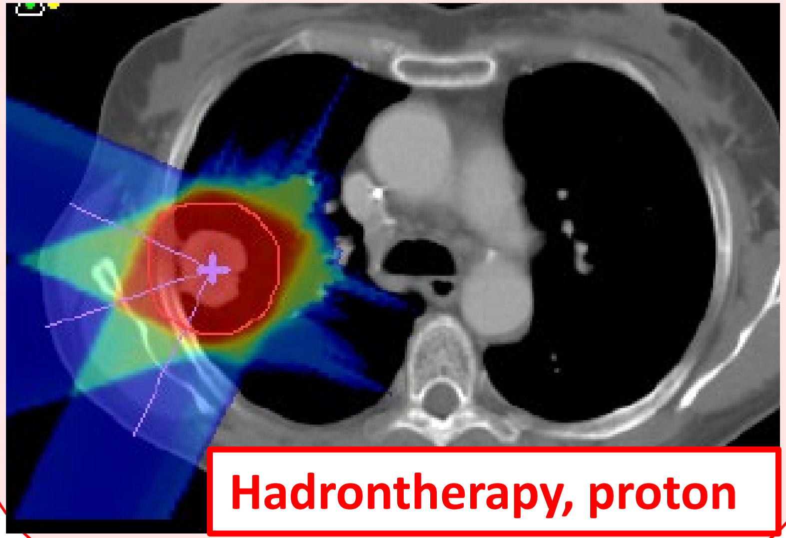


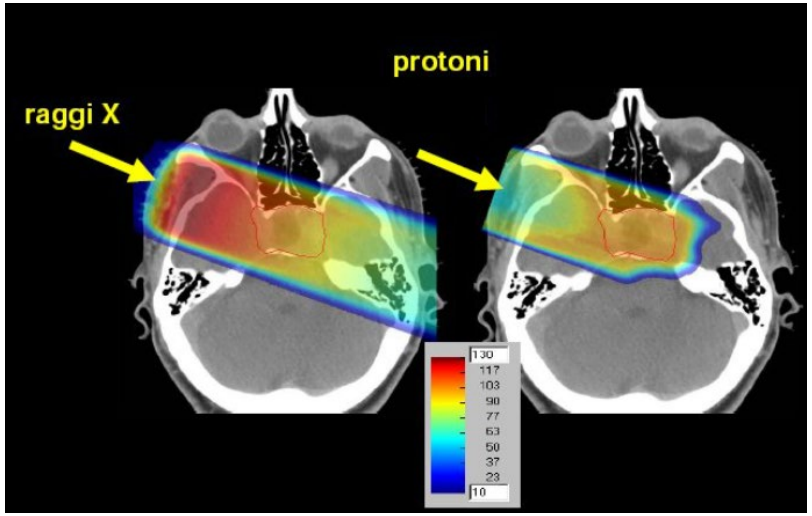
CNAO

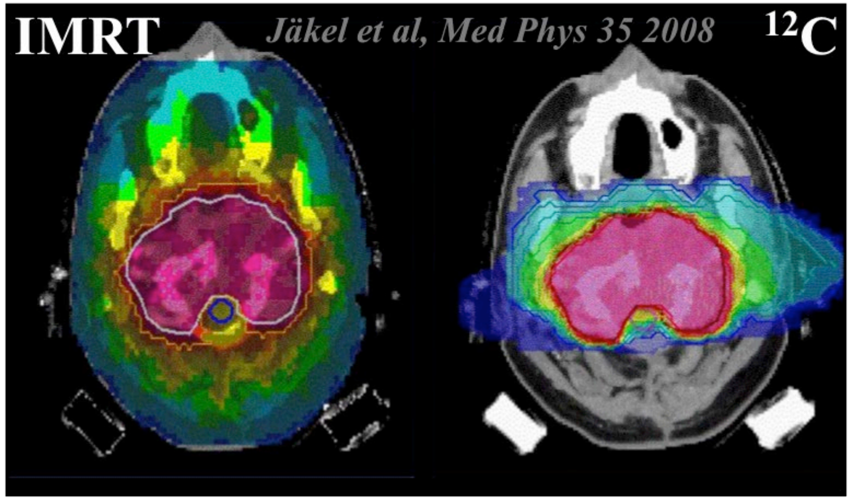


Dose profiles: radio vs hadro



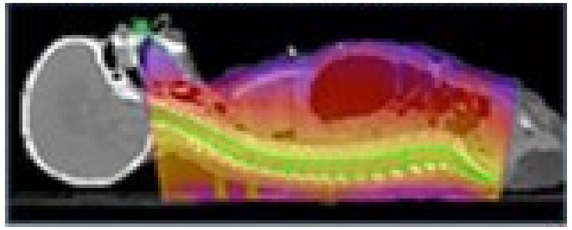


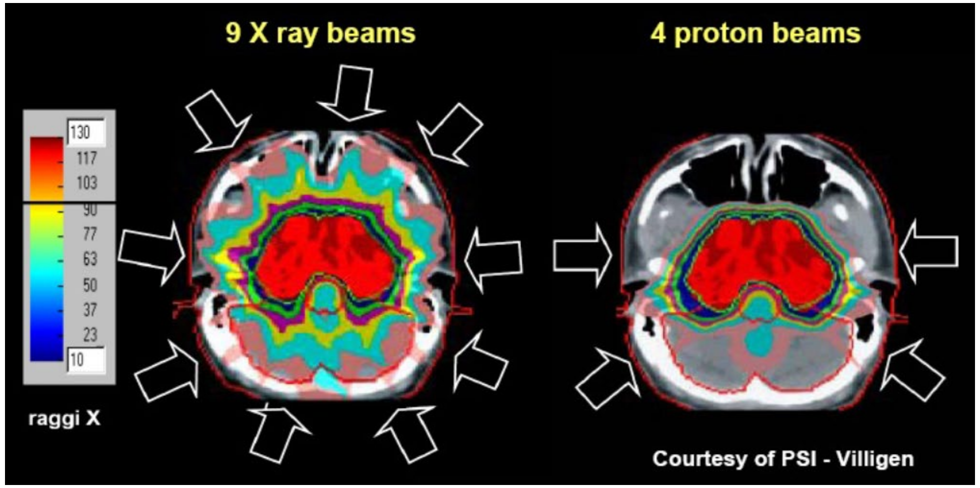




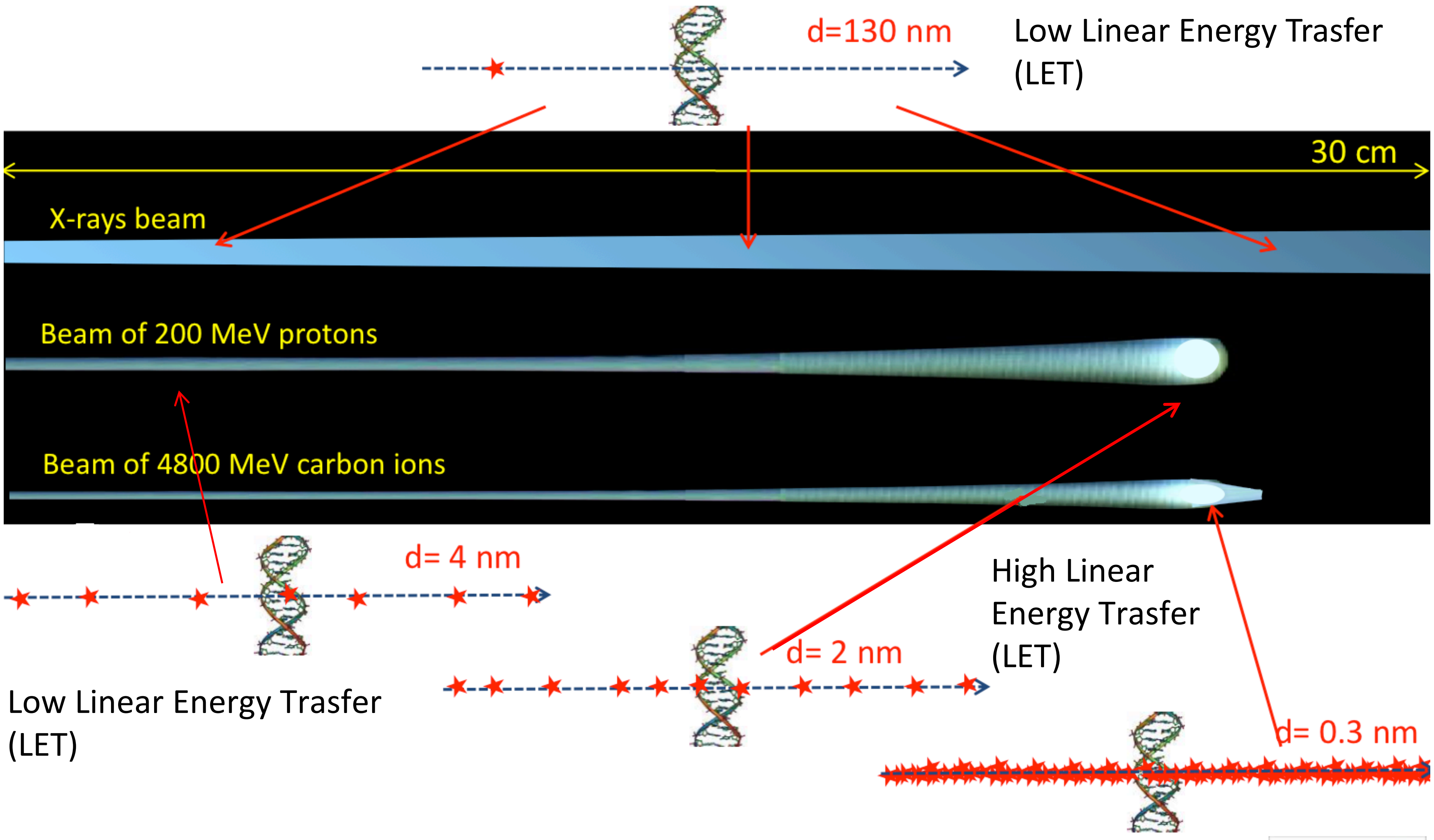
HADRONTHERAPY

CONVENTIONAL RADIOTHERAPY

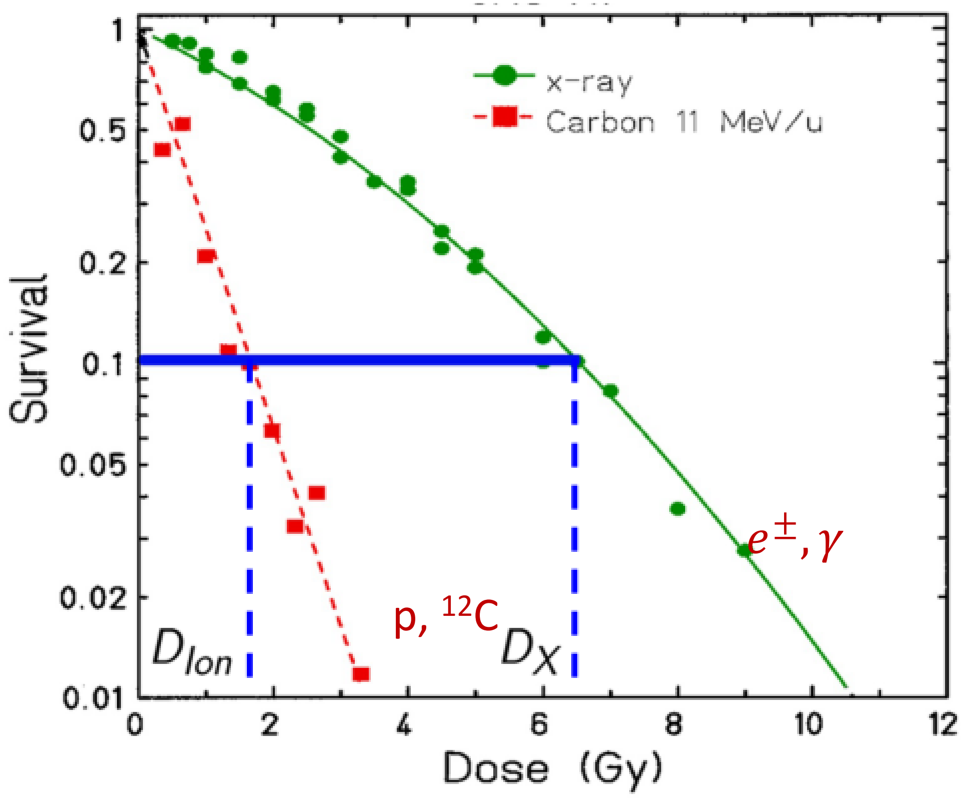




Different bullets, different effects



Dose vs particle type: RBE and fractioning



WK Weyrather, G Kraft - Radiother Oncol. 73-2 (2004)

- Relative biological effectiveness

$$RBE_n = \left.\frac{D_X}{D_{ion}}\right|_{S_X = S_{ion} = n}$$

RBE ~ 1.1 for protons

RBE > 1 for ions

- Healthy tissues recover faster than tumor cells
- Treatments are usually done in several steps
  → fractioning
- 20-40 treatments for doses from 20 to 80 Gy
  (LETHAL DOSE if given in one shot!)

How the fraction dose is chosen

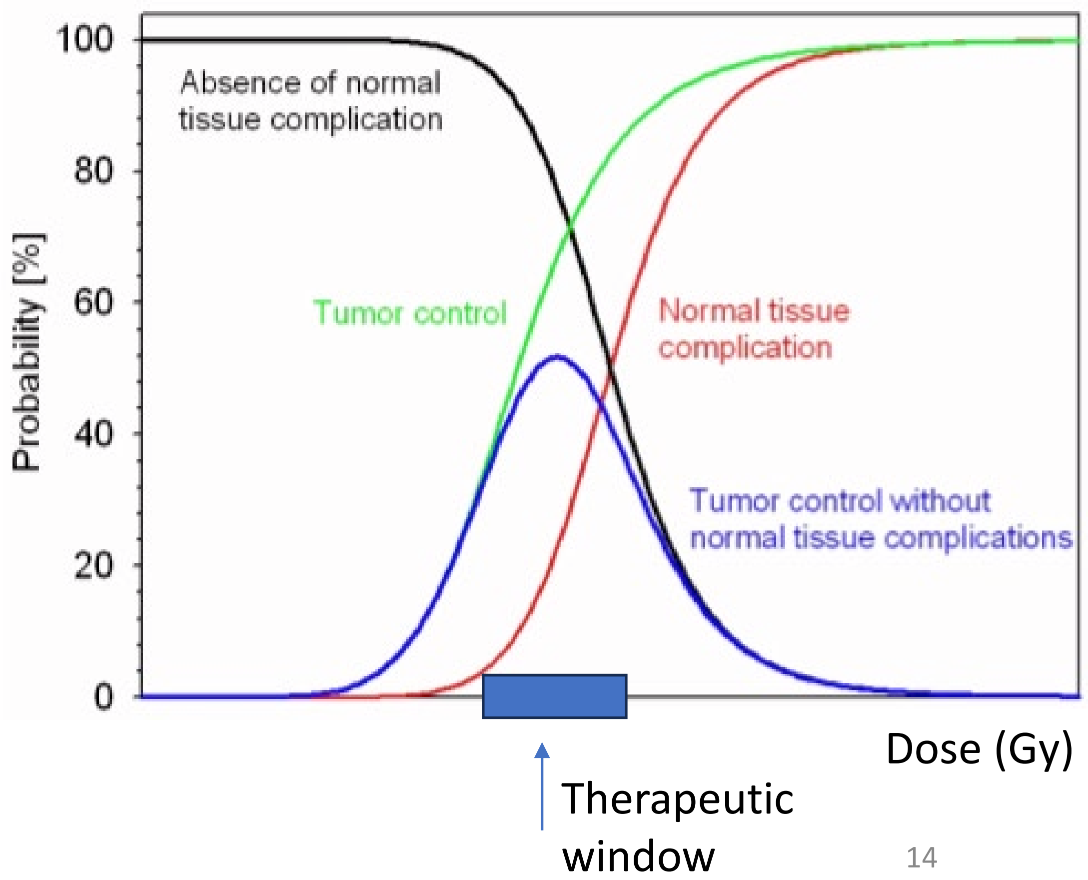
Tumor Treatment:

- **TCP** (Tumor Control Probability): probability to control the tumor → MAXIMIZE
- **NTCP** (Normal Tissue Complication Probability): probability to have complication in the healthy tissue → MINIMIZE

TCP & NTCP increase with the dose

Find the dose range to maximize the TCP - NTCP

Typical dose fraction: 2 Gy/treatment
Each treatment lasts for few minutes
(2 minutes typically)



tolerance

- Quantity: 5-7%
- Space: 3mm

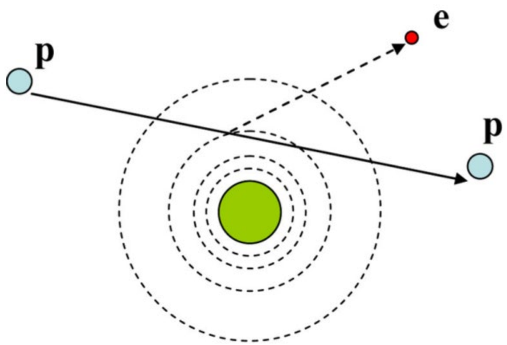
Stopping power: Bethe-Block range

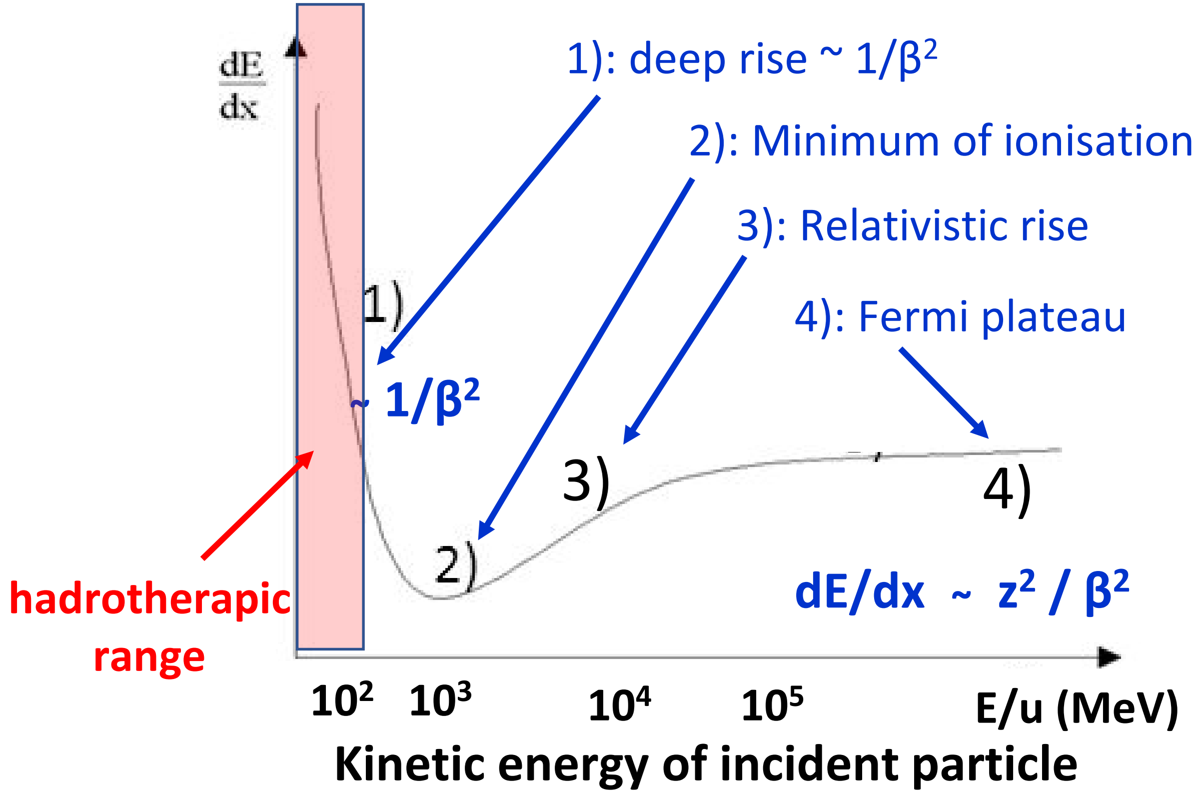
$$-\frac{dE}{dx} = \frac{\rho Z}{A}\,\frac{4\pi N_A m_e c^2}{M_U}\left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2 \frac{z^2}{\beta^2}\left[ln\left(\frac{2m_e c^2\beta^2}{I(1-\beta^2)}\right)-\beta^2-\frac{\delta}{2}-\frac{C}{Z}\right]$$

Medium properties **General constants** **Beam characteristics (z, β)** **Corrections**

Main energy loss: ionization of medium atoms.
Derived for the condition (almost free electron):

$$v_p \gg v_e \approx \alpha\, c$$





Stopping power: the low energy range

What happens when $v_p \approx v_e \approx \alpha\, c$ or $v_p < v_e$?

No more approximations:
- Atom energy levels are perturbed by the passing Ion
- Ion recoils against the atom!

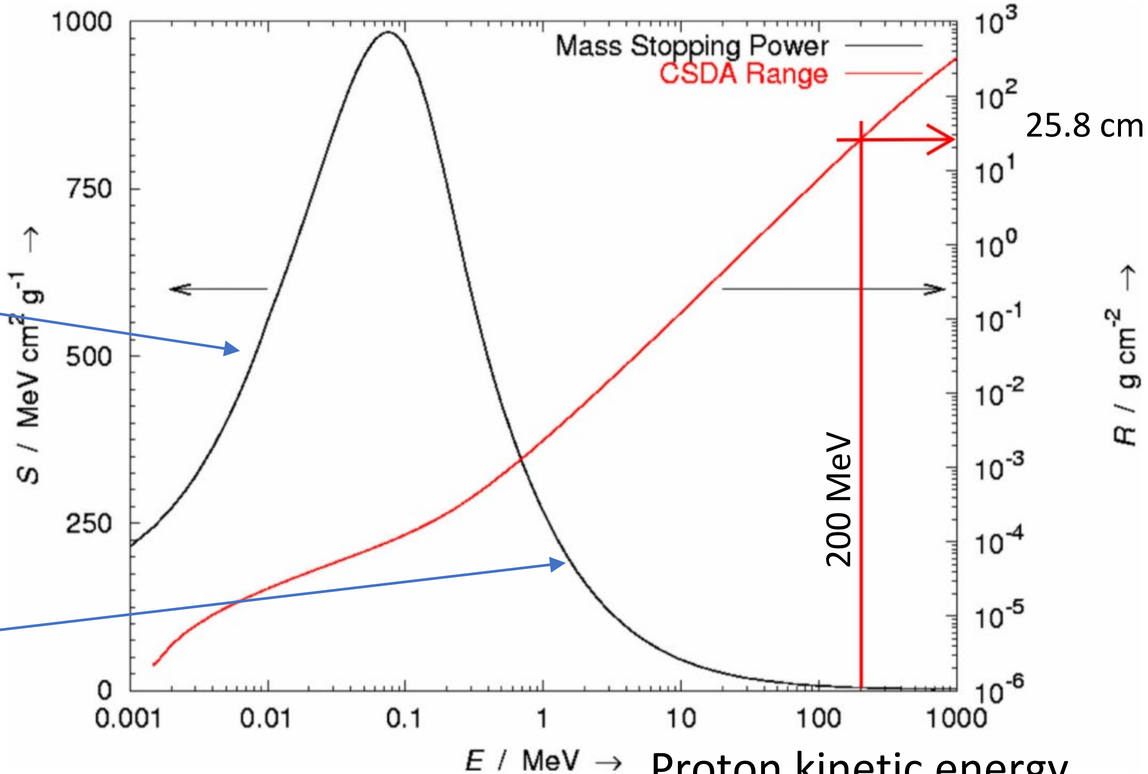
$$S_L = -\frac{dE}{dx} = \alpha\, E^{\beta}$$

with α and β dependent on medium and ion charge
First approximation: $\beta \approx 0.5 \quad \rightarrow S_L \propto v_p$!

Fenomenological combination of
High Energy (Bethe-Block: S_H)
and Low Energy (S_L) regimes:

$$\frac{1}{S} = \frac{1}{S_H} + \frac{1}{S_L} \quad \rightarrow \quad S = -\frac{dE}{dx} = \frac{S_H S_L}{S_H + S_L}$$

Stopping power for protons in water

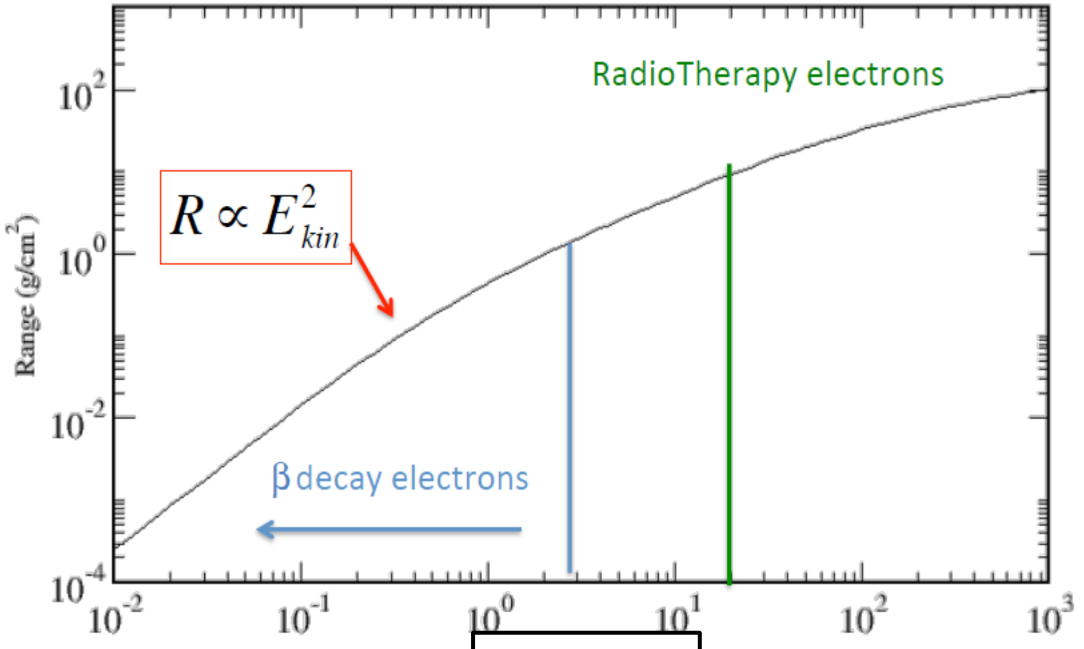


Peak stopping power S_{peak},
braking force : $S_{peak} = \mathrm{F} \approx 16$ nN

Path range

Range : depth at which half of protons-ions come to rest

$$R = \int_0^R dx = \int_0^{E_0} \frac{dE}{\frac{dE}{dx}} = \ \dots \ \approx E_0^2 \text{ or better } = \ E_0^{1.75}$$



In general

$R(E) = \alpha E^p$

α depends on material,
p on Energy

Range of charged particles depends on their kinetic Energy → very useful in hadrontherapy

Possibility to go to deeper region of the human body just changing the beam energy

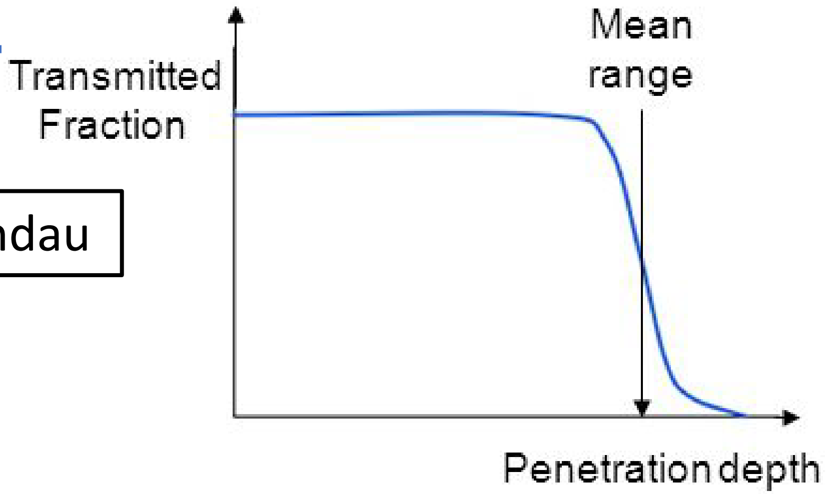
If the material is a compound → Bragg additivity rule

$$\left(\frac{dE}{d(\rho x)}\right)_{tot} = \frac{\sum_i \rho_i \left(\frac{dE}{d(\rho x)}\right)_i}{\rho_{tot}}$$

Energy loss and range fluctuations

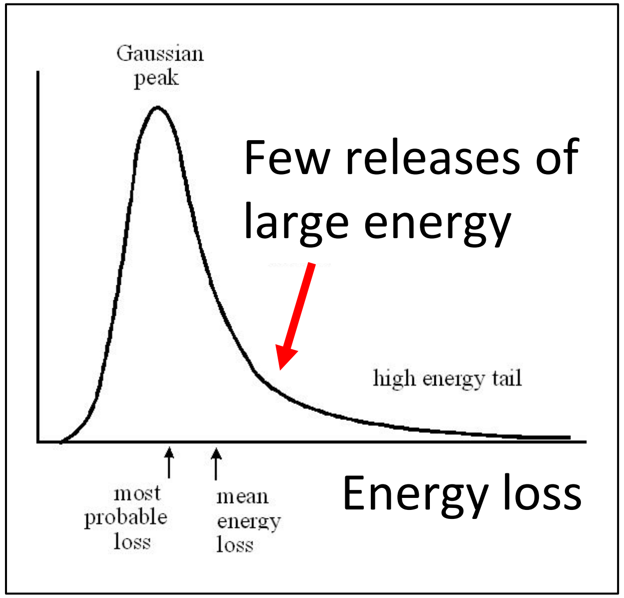
dE/dx is a stochastic process (hundreds of interactions)

Energy loss distribution is not a Gaussian around a peak, but it is a Landau



dE/dx Fluctuation → Range fluctuation

Width depends on projectile and on material



Example proton 200 MeV in water

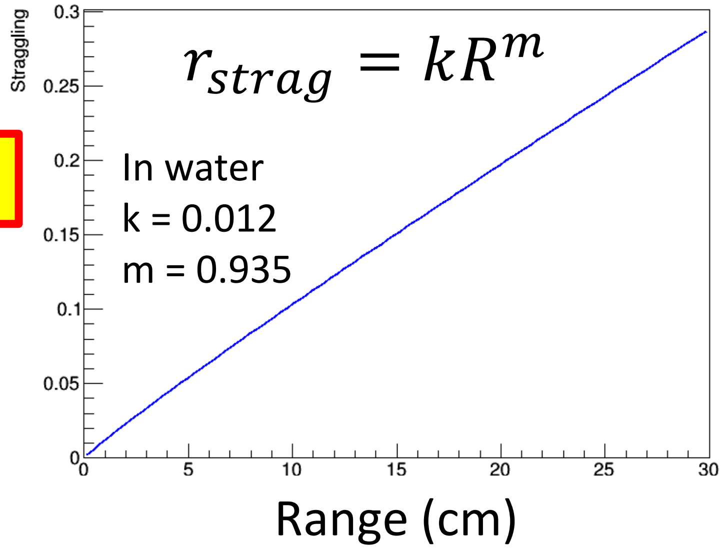
- Range = 25.8 cm
- Range fluctuation (RMS) = 2.5 mm (1%)

Range straggling important in hadrontherapy

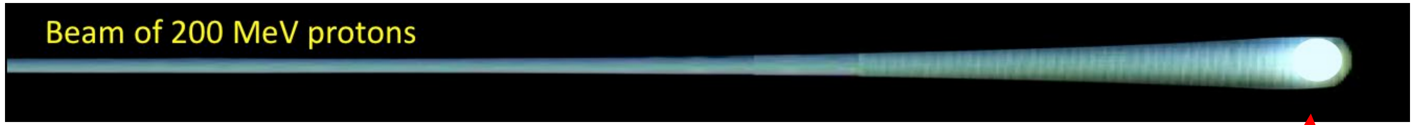
↓

Different depth of the treatment

Range straggling (cm)



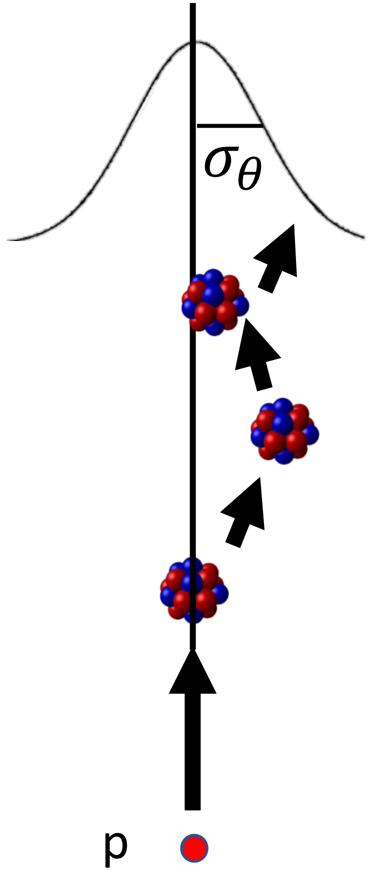
Lateral straggling



$$F(\theta, x) = \frac{1}{2\pi\sigma_\theta} e^{-\frac{\theta^2}{2\sigma_\theta^2}}$$

Gaussian shape around the direction of incident particles

total effect of a large number of independent small-angle scattering



$$\sigma_\theta = \frac{13.6\ MeV}{\beta c p} Z_p \sqrt{\frac{x}{x_0}} \left[1 + 0.038 ln\left(\frac{x}{x_0}\right) \right]$$

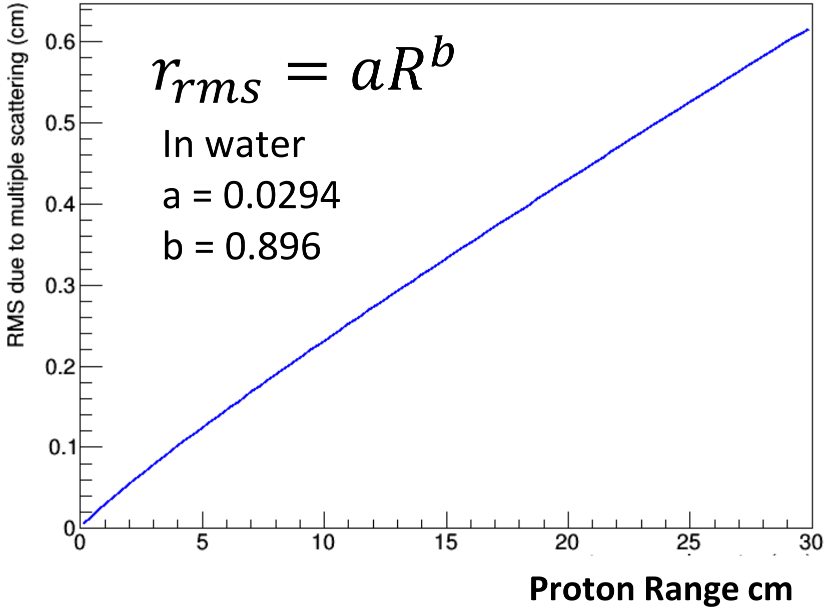
Z_p Charge of incident particle

p Momentum of incident particle

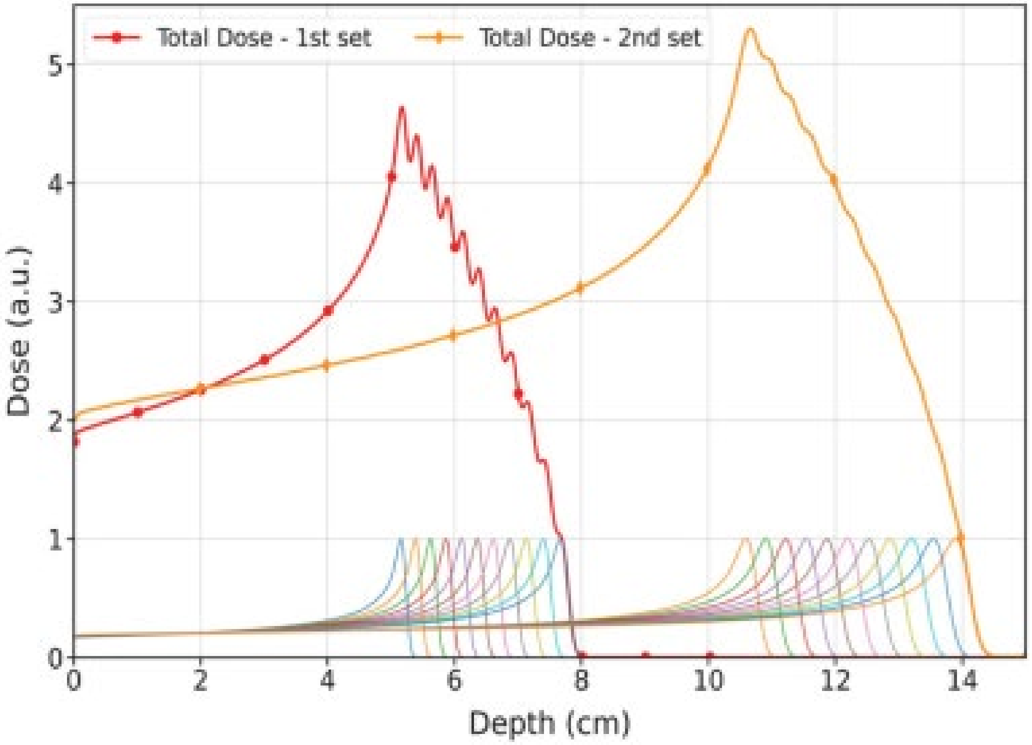
$\frac{x}{x_0}$ crossed material in units of radiation length

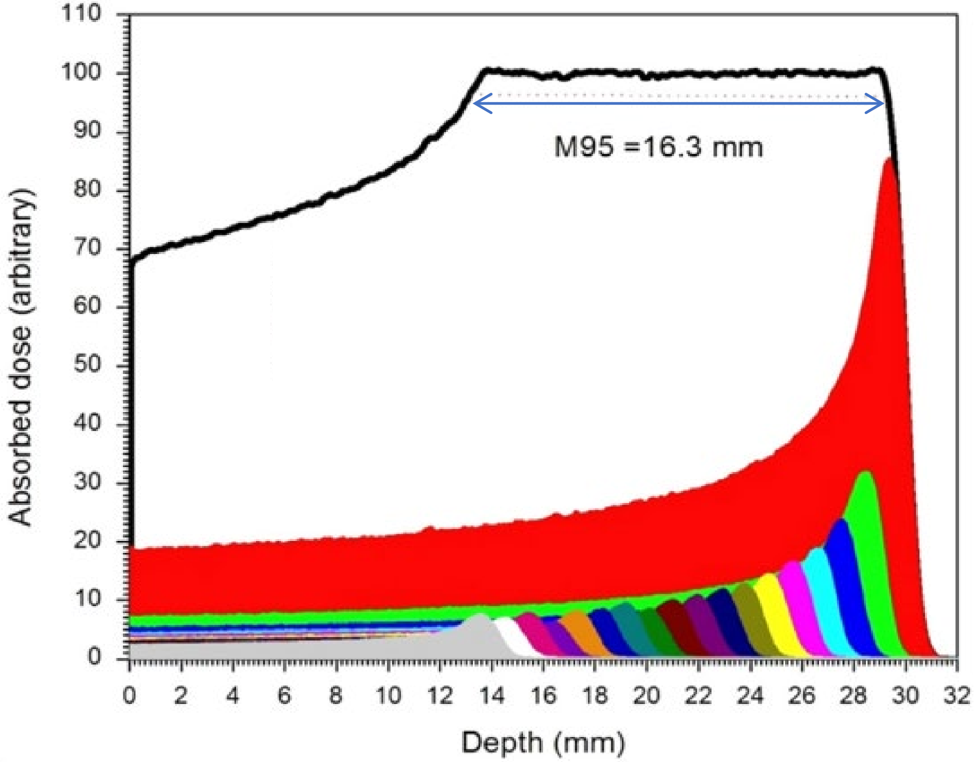
Width of material to reduce the particle energy of 1/e

Rms of the lateral displacement (cm) at the stopping point

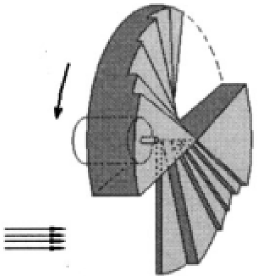


Spread out Bragg peak: range fluctuations





p, E=220 MeV



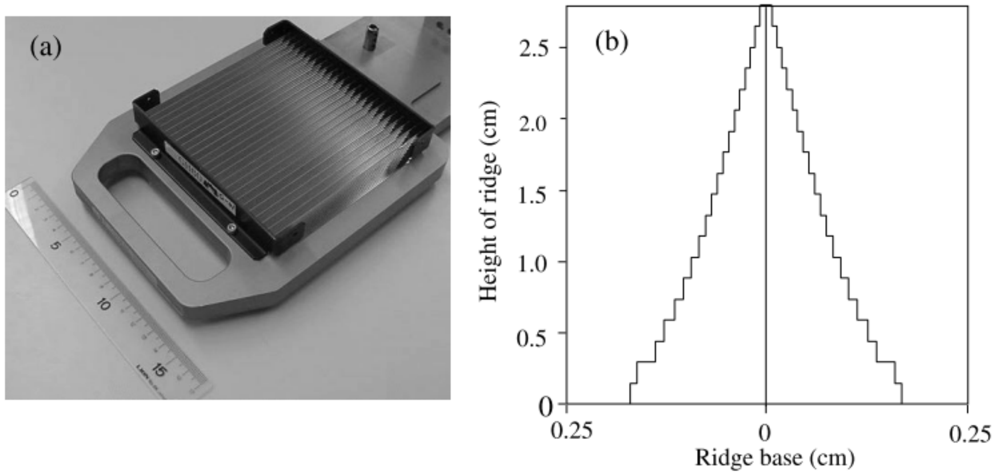
p, E< 220 MeV

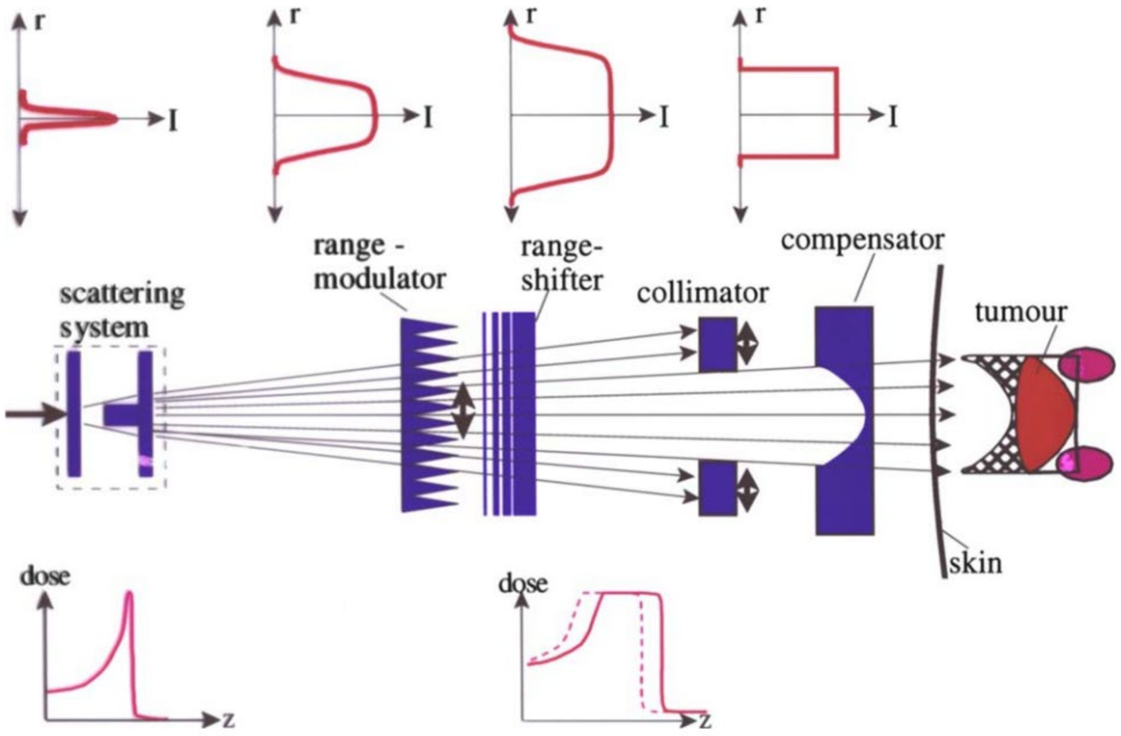
Ridge filters: taking advantage of lateral spread

Ridge filters have crests smaller than the beam size

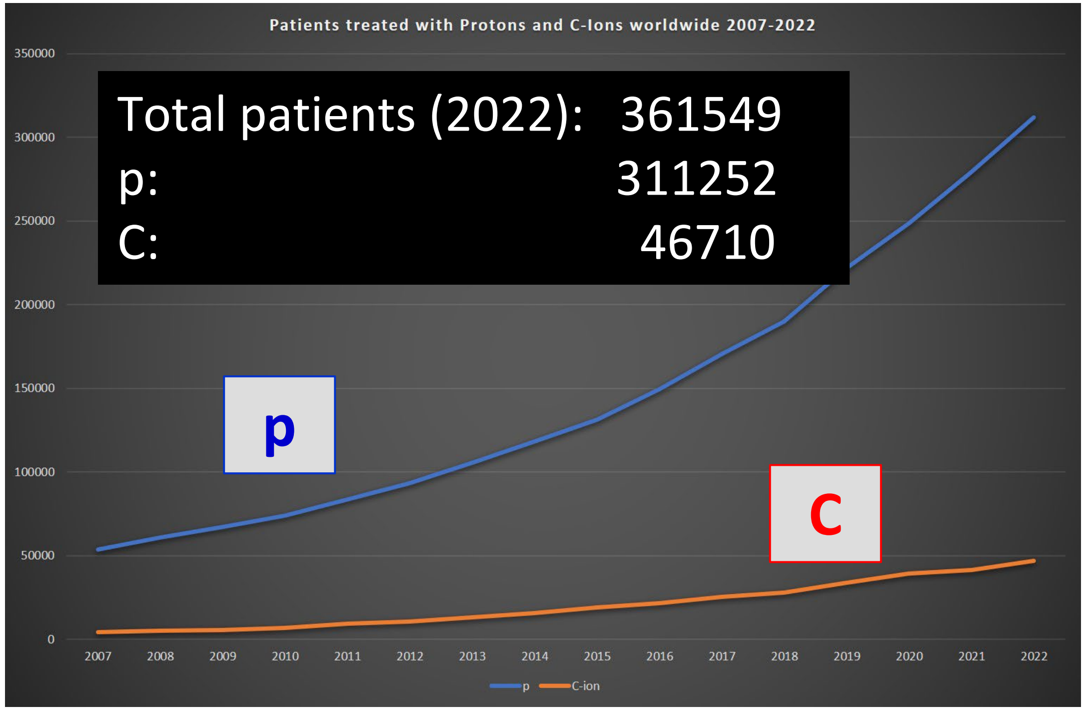
They are tuned to form passively a Spread-Out Bragg Peak

Beam lateral size





Distribution of treatment centers in the world



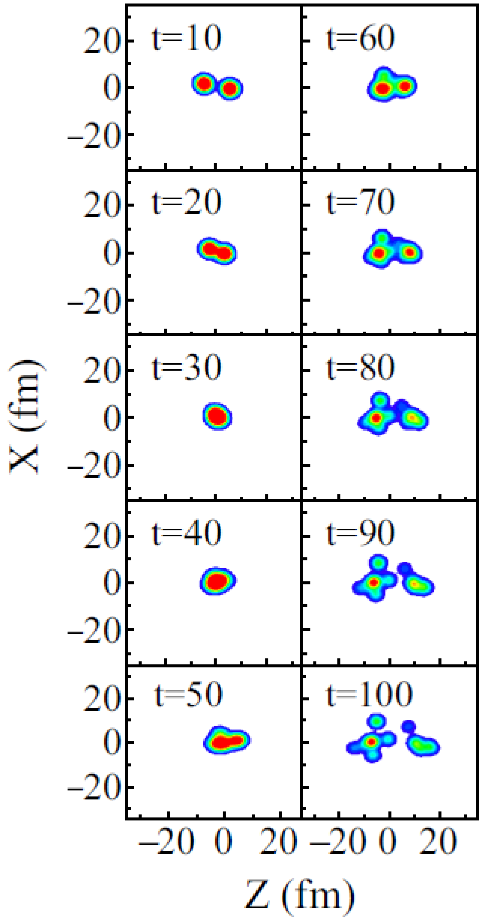
p

(p & C)

Data for Hadrontherapy machines only!
Flash therapy is not yet a stable clinical practice!

Nuclear effects in hadron therapies

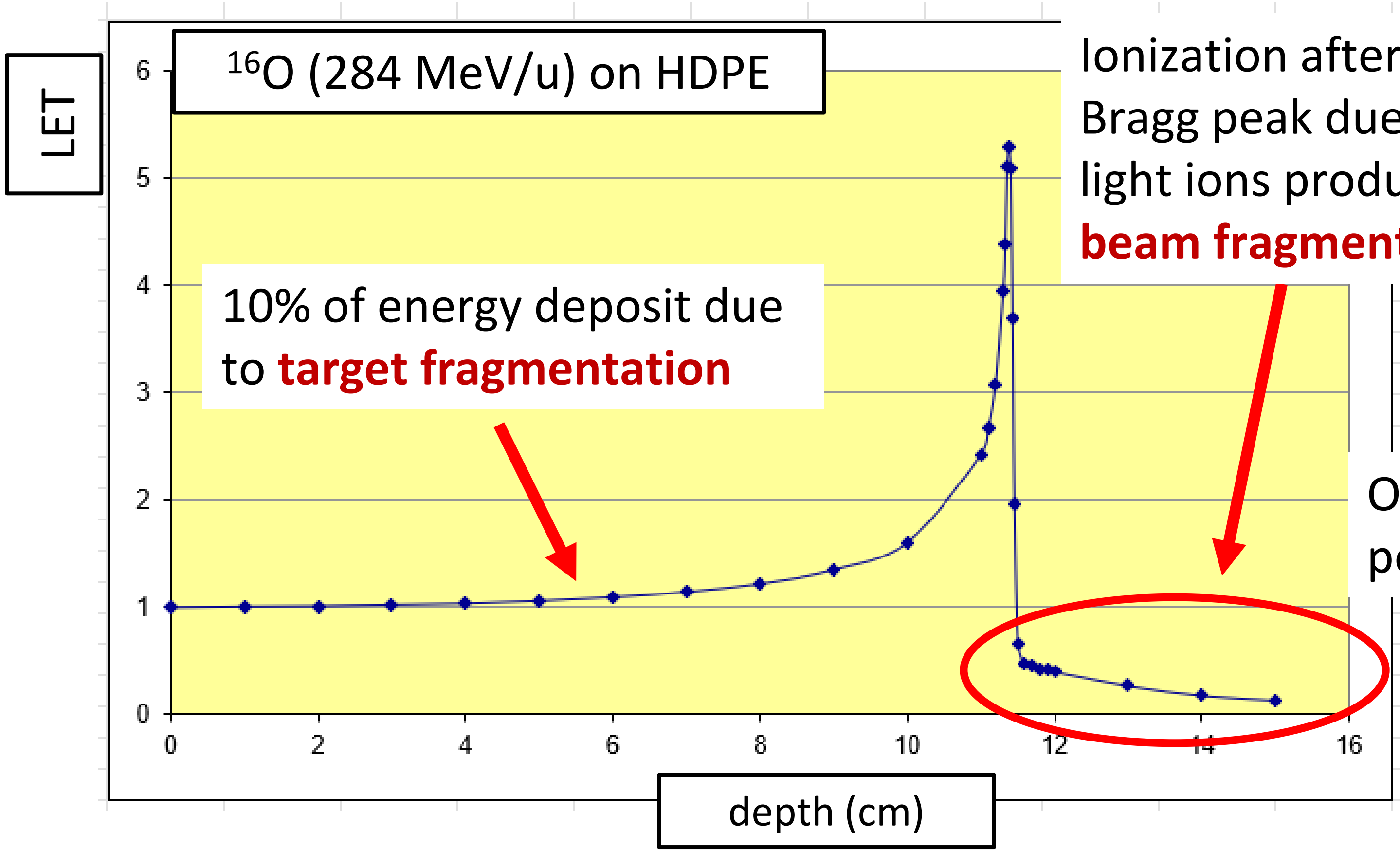
$^{12}C + ^{12}C$ @ 95 MeV/n



Main effect: Fragmentation i.e. production of ligher nuclei

Target fragmentation → local ionization

Beam fragmentation → longer path

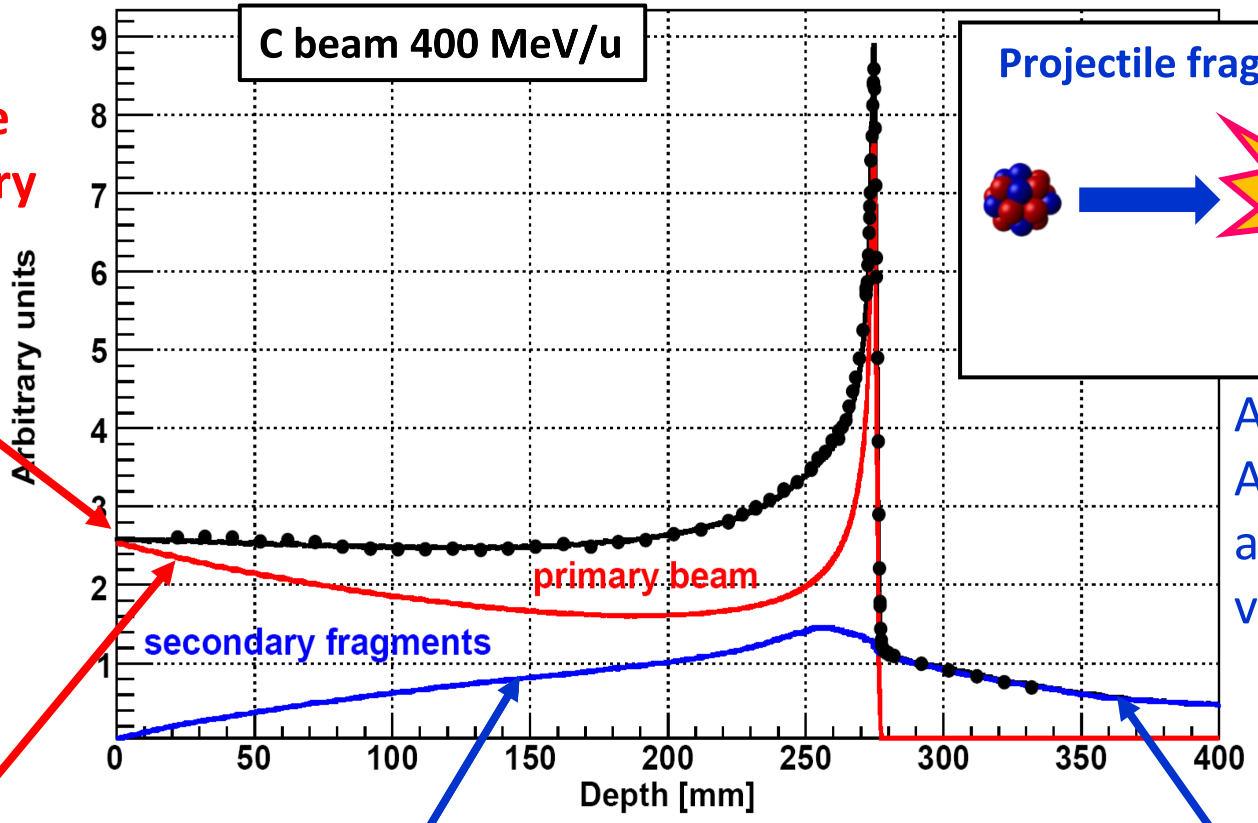


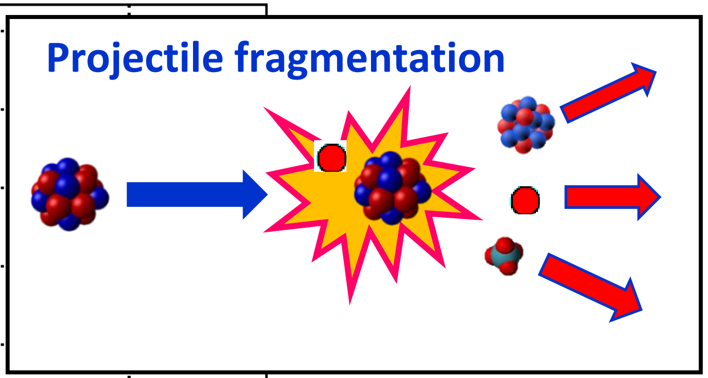
Ionization after the Bragg peak due to light ions produced in **beam fragmentation**

Organ at risk position?

Projectile fragmentation

At the entrance there are all particles of the primary beam (in this case C)





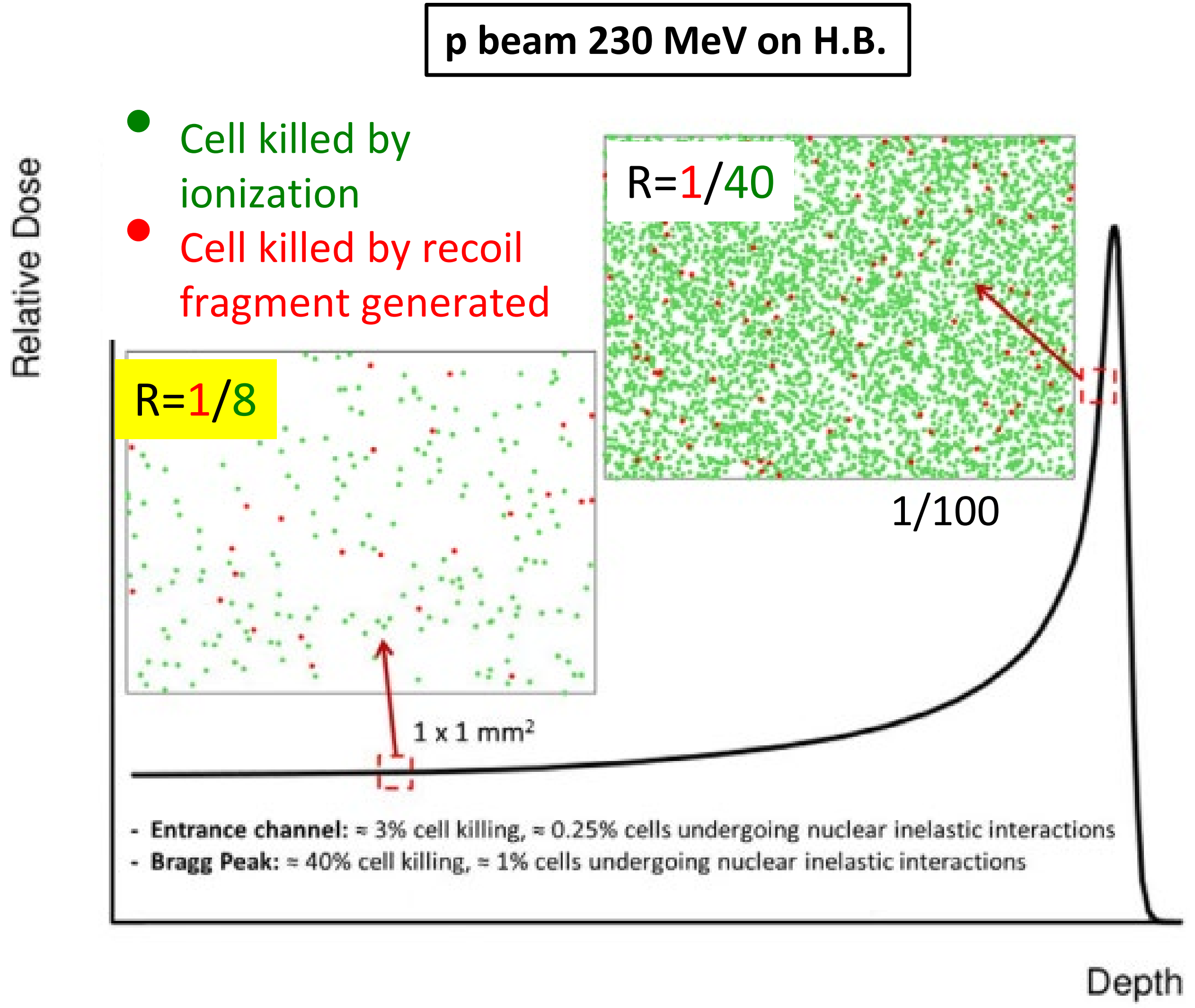
About same Ekin/A
All fragment have about the same velocity

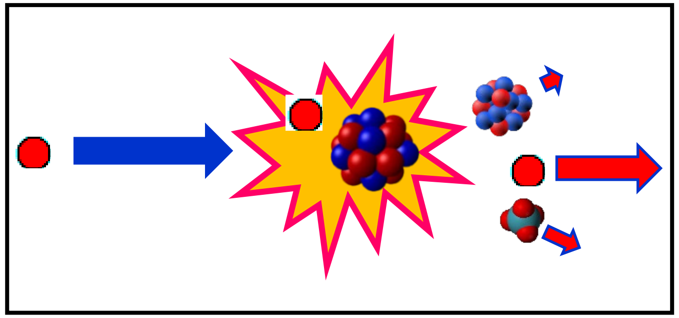
Number of primary particles decreases (→ decrease deposited energy) due to nuclear interaction (projectile fragmentation)

Number of secondary particles increases (→ deposited energy)

(projectile fragmentation → lower Z → lower dE/dx → larger range → beyond cancer volume

Target fragmentation





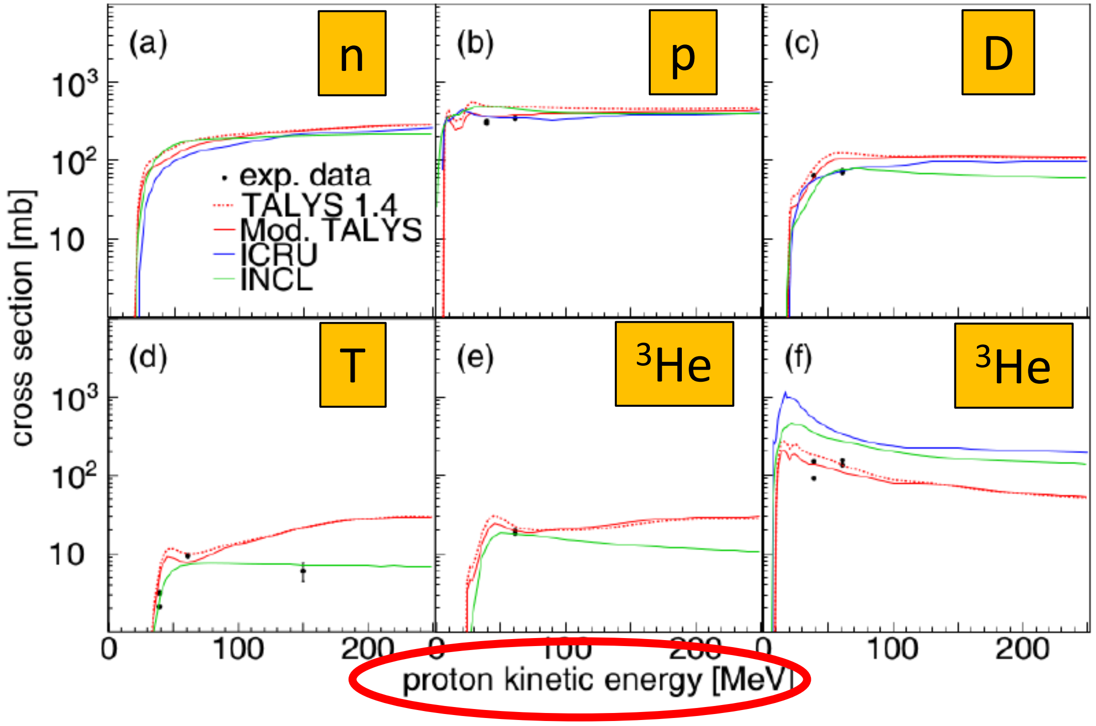
About same Ekin/A of the target i.e. 0

Down here target fragmentation of a 180 MeV p on H_2O

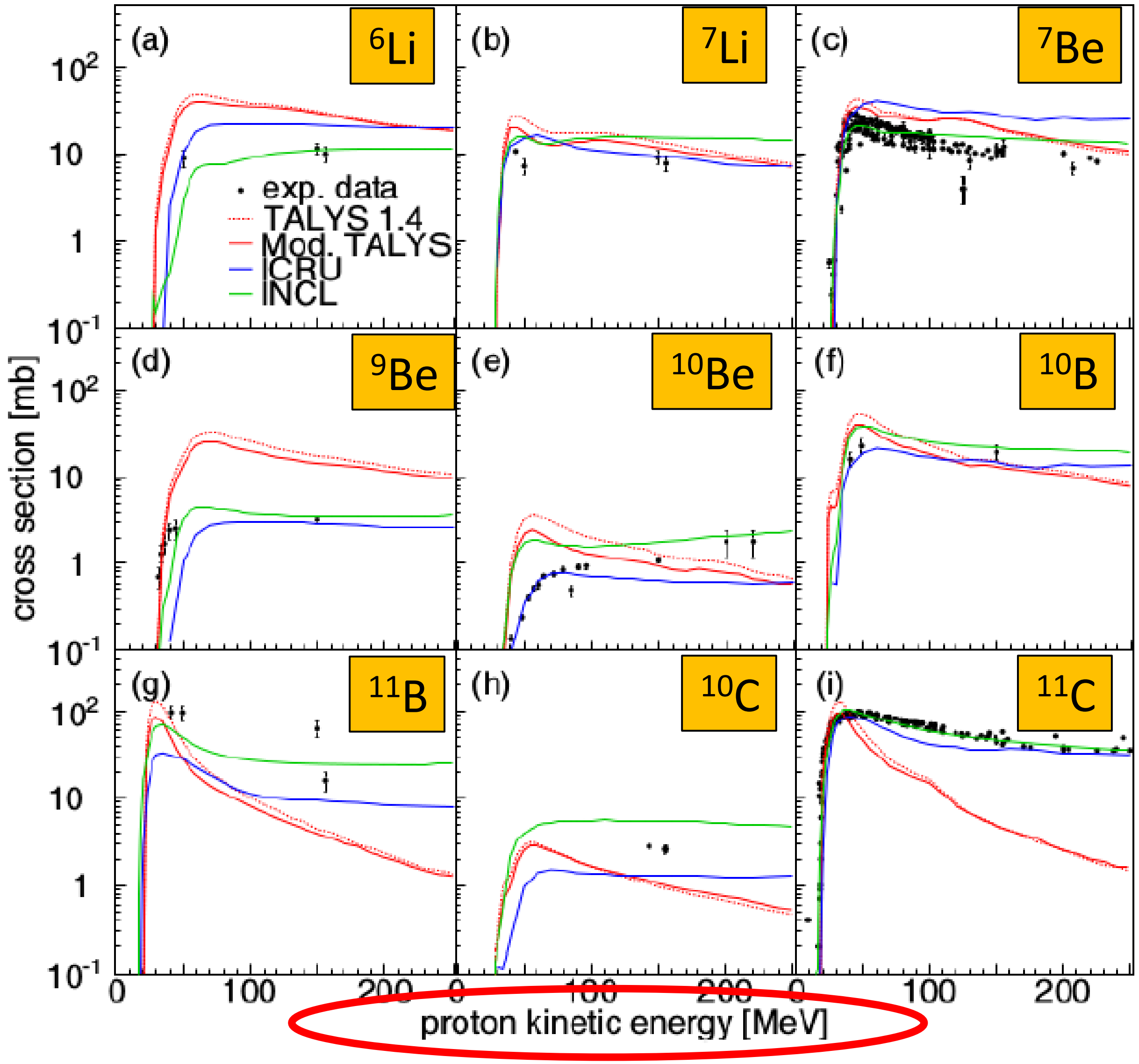
Fragment	E (MeV)	LET (keV/µm)	Range (µm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

Experimental Nuclear proton cross section: p + $^{12}C \rightarrow X$

Production of different fragment

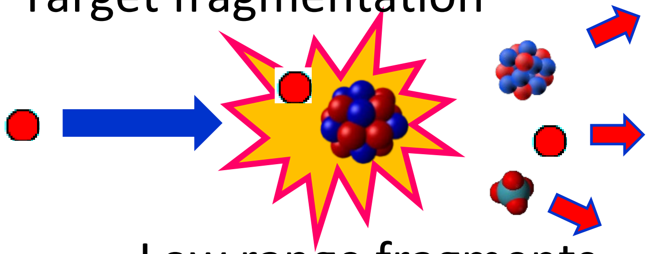


Useful to measure σ of each produced fragment wrt its energy (not beam energy)



Inverse kinematics

Target fragmentation



Low range fragments

p + C,O → fragments

Lorentz transformation

→ measure **beam direction (x, y, z)**

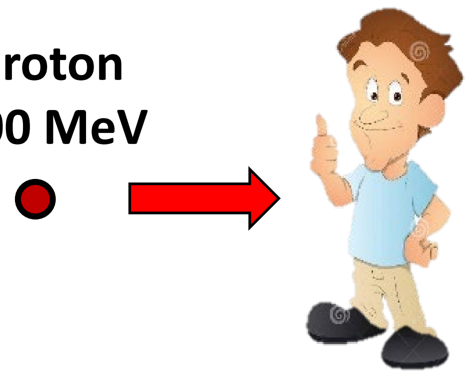
$$\begin{pmatrix} ct' \\ x' \\ y' \\ z' \end{pmatrix} = \begin{pmatrix} \gamma & 0 & 0 & -\beta\gamma \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ -\beta\gamma & 0 & 0 & \gamma \end{pmatrix} \cdot \begin{pmatrix} ct \\ x \\ y \\ z \end{pmatrix} = \begin{pmatrix} \gamma ct - \beta\gamma z \\ x \\ y \\ -\beta\gamma ct + \gamma z \end{pmatrix}$$

Impossible to detect fragments

DIRECT KINEMATIC

p + C,O → fragments

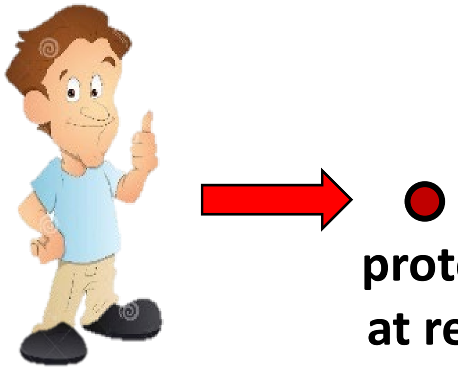
proton
200 MeV



C,O at rest

INVERSE KINEMATIC

C,O + p → fragments

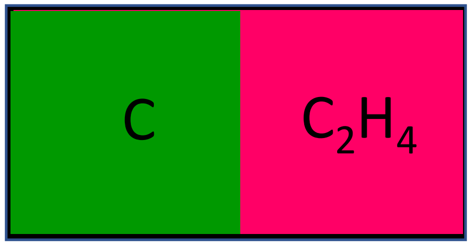


C,O 200 MeV/A

proton
at rest

Target: H at rest

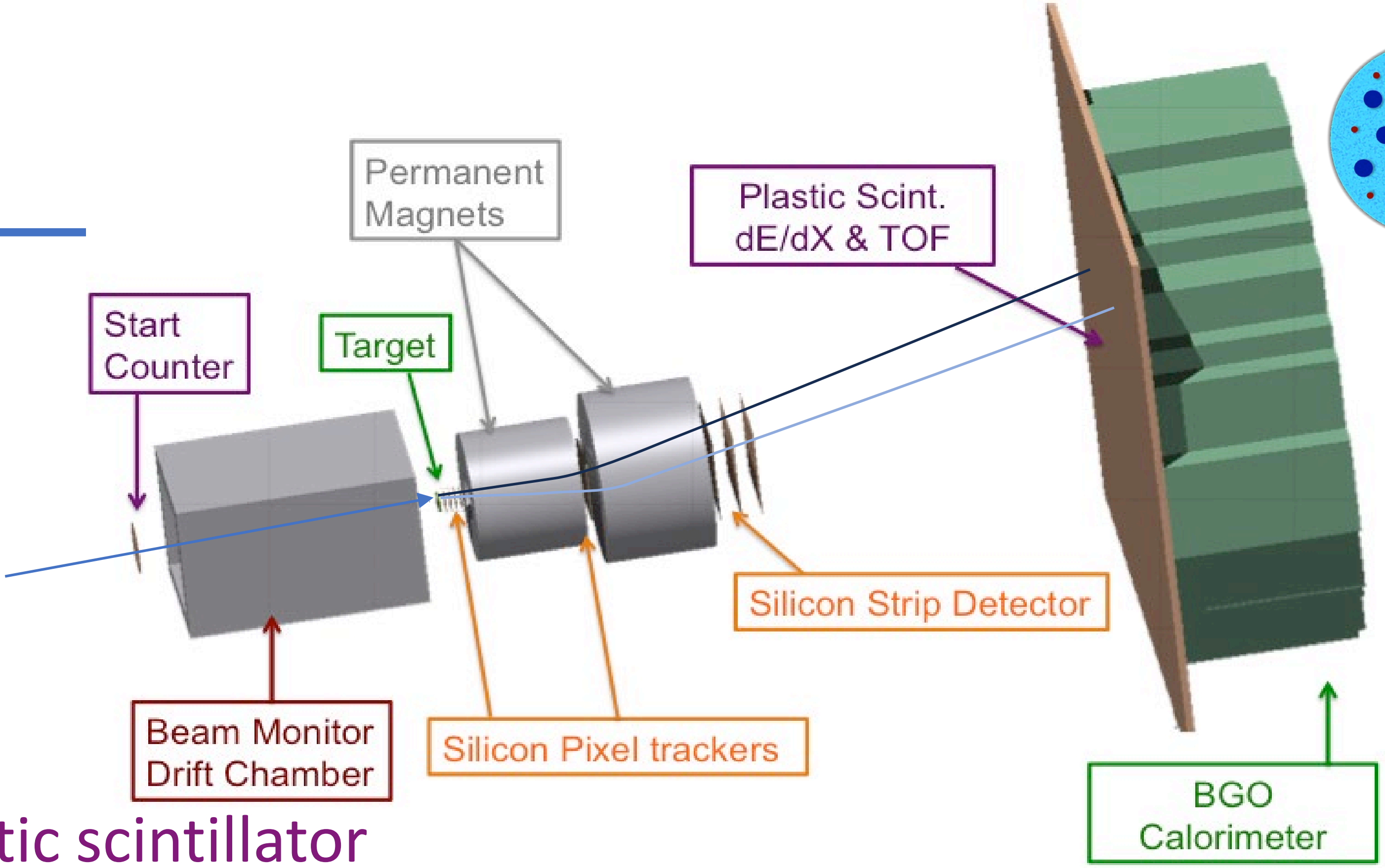
Target (2mm)



$$\frac{d\sigma}{dE_{kin}}(H) = \frac{1}{4}\left(\frac{d\sigma}{dE_{kin}}(C_2H_4) - 2\,\frac{d\sigma}{dE_{kin}}(C)\right)$$

FOOT Detector

For the fragment with Z>2 measurements of TOF, P, Ekin, DE



- ✓Start Counter = thin plastic scintillator
- ✓Beam Monitor = drift chamber
- ✓Vertex detector & Intermediate Tracker = monolithic silicon pixel detector
- ✓Large tracker = silicon strip detector
- ✓DE/TOF Detector = plastic scontillator
- ✓Calorimeter = BGO crystal calorimeter

Expected target fragmentation performances:

σ_p/p ~ 5%

σ_{TOF} ~ 100 ps

$\sigma_{Ekin}/Ekin$ ~ 1-2%

$\sigma_{\Delta E}$ ~ 2%

FOOT Experiment

p + C, O, N
C + C, O, Si
Fe + C, Si, Al

$$\frac{d\sigma}{d\Omega}, \frac{d\sigma}{dE_{kin}}$$

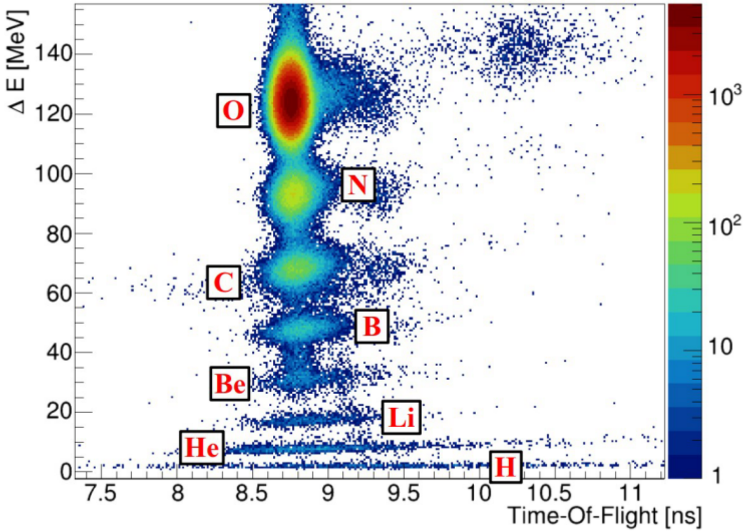
Goal accuracy <5%

Electronic set-up results (selection)

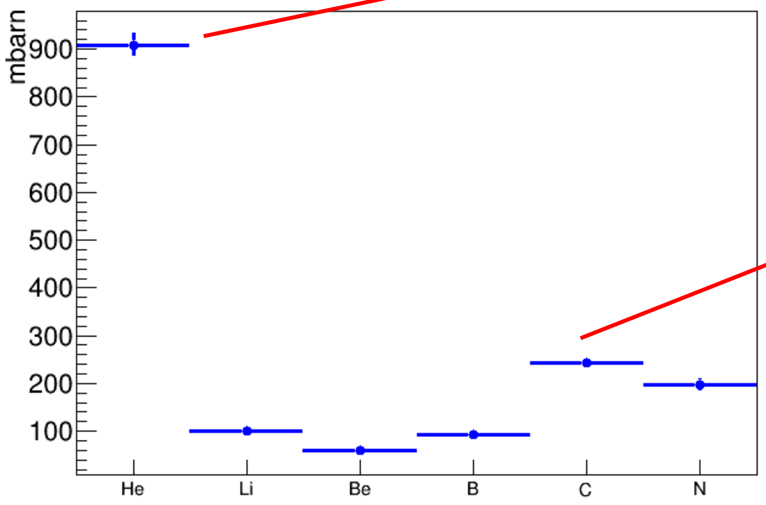
Measurements at GSI, Beam: ^{16}O, 400 MeV/N, Target: C

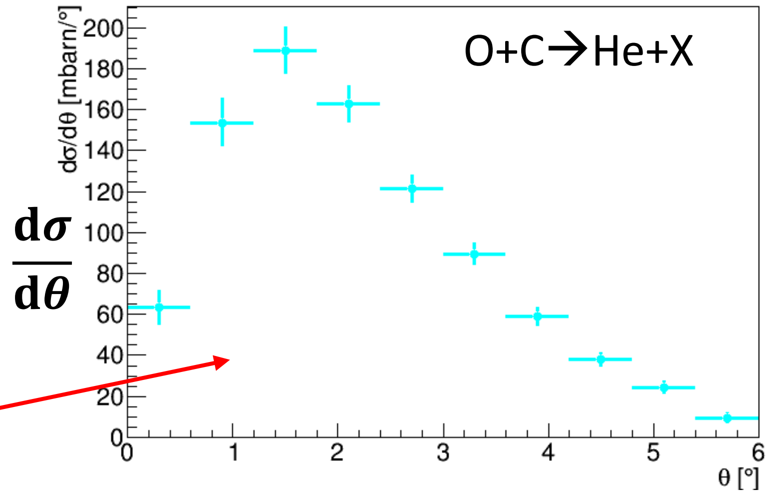
Results from first engineering runs (no tracking sensors included)

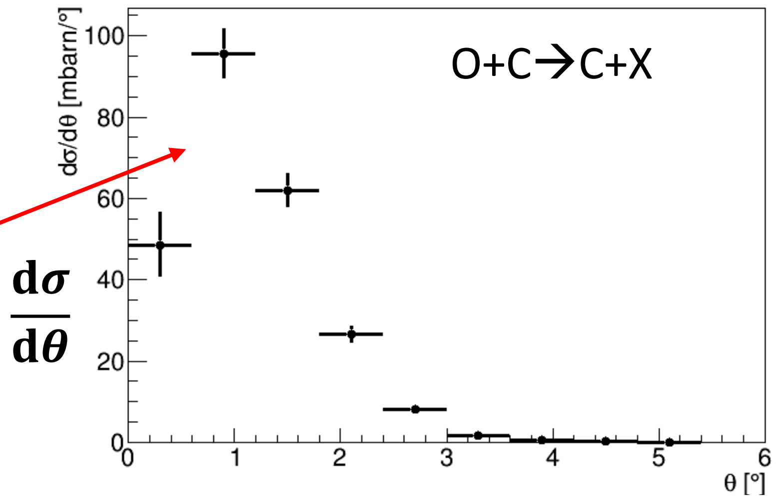
Particle identification



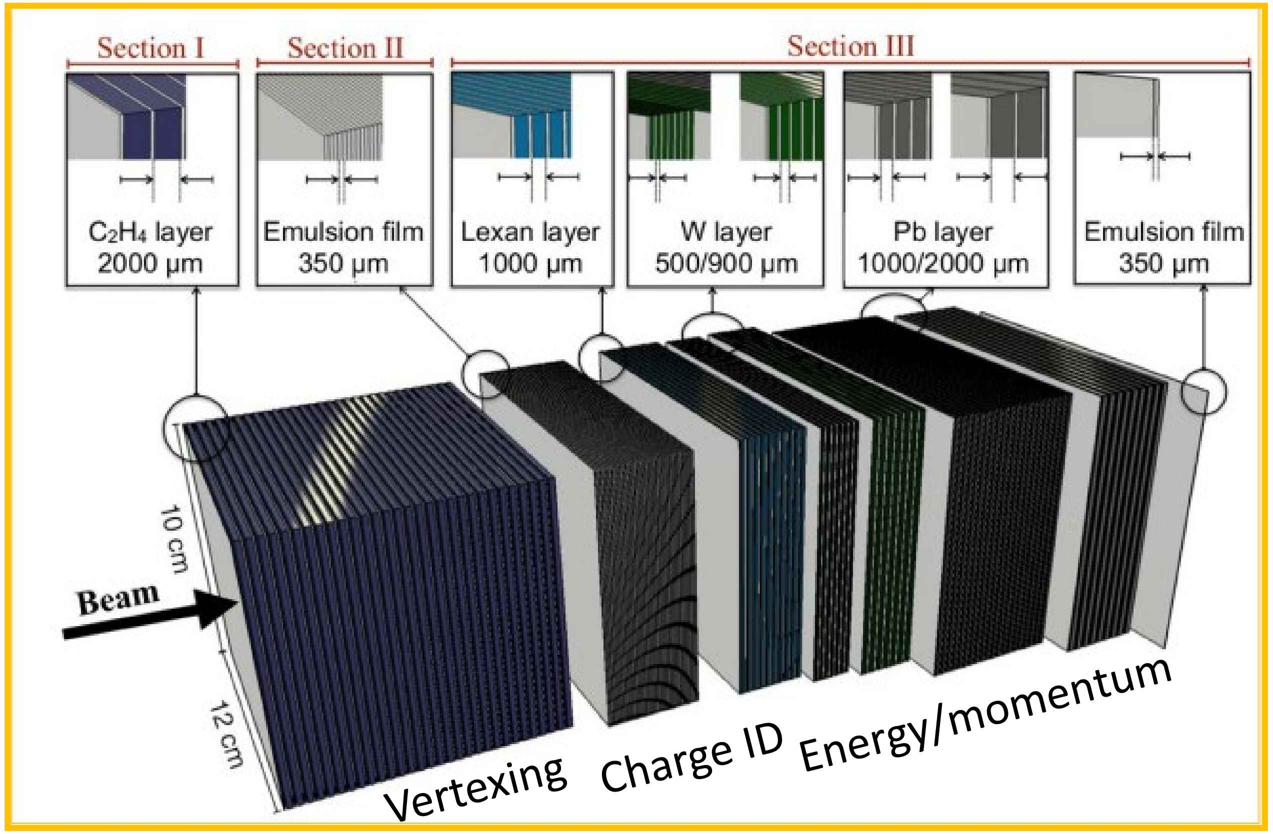
Production cross section for specific elements



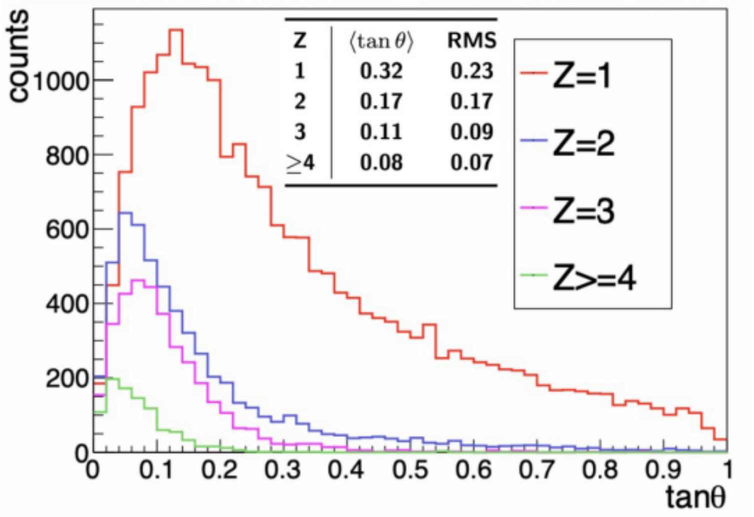




Emulsion set-up

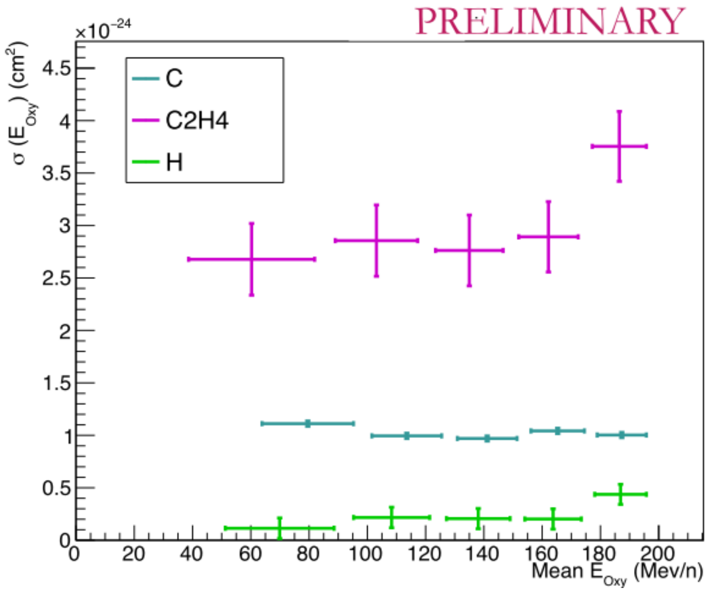


^{16}O, 400 MeV/N on C



^{16}O, 200 MeV/N on C, C_2H_4

Total reaction cross section



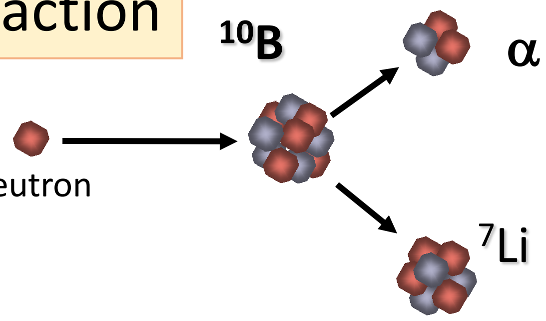
Two target technique to extract cross sections on H

$$\sigma_H = \frac{1}{4}(\sigma_{C_2H_4} - 2\sigma_C)$$

Boron Neutron Capture Therapy (BNCT)

Break-up reaction

$^{10}B[n,\alpha]^{7}Li$ reaction



$n + {}^{10}B \rightarrow {}^{7}Li^{*} + {}^{4}He \rightarrow {}^{7}Li + {}^{4}He + 0.48\ \text{MeV}\ \gamma + 2.3\ \text{MeV}\ (93\%)$

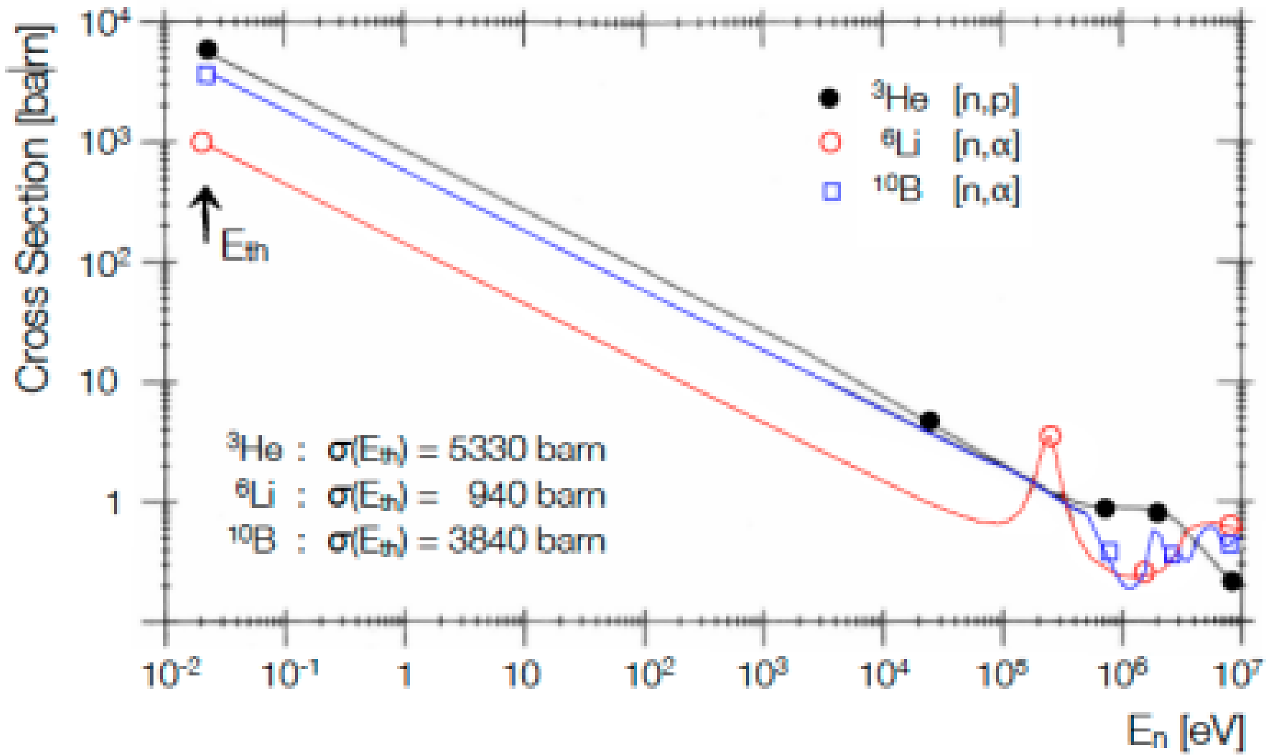
$\rightarrow {}^{7}Li + {}^{4}He \quad + 2.8\ \text{MeV}\ (7\%)$

^{10}B is about 20% in the natural boron

Cross section

$$\sigma(E) = \sigma(E_{\rm th}) \cdot \frac{v_{\rm th}}{v}$$

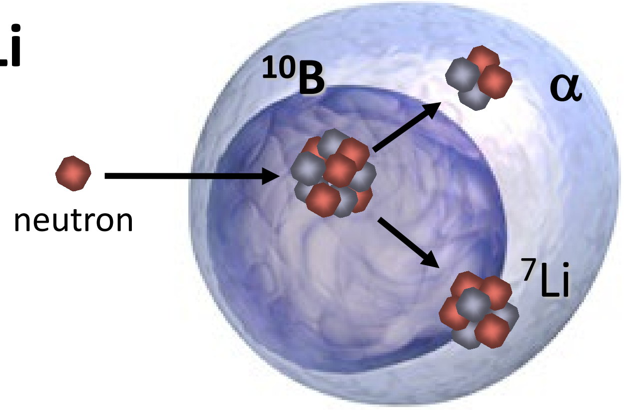
$$\sigma_{^{10}B}(E_{\rm th}) = 3940\ \text{barn}$$

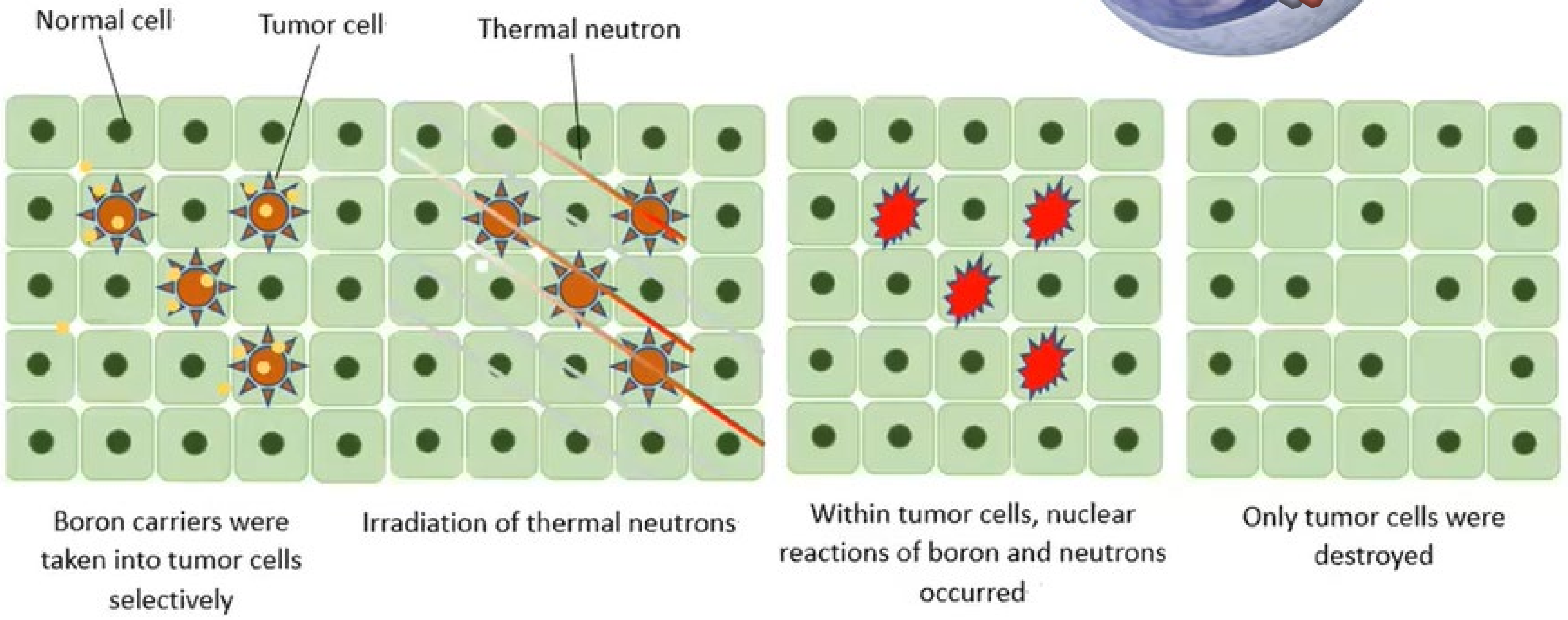


Boron Neutron Capture Therapy (BNCT)

Fragment ranges are of the order of the cell size → highly localized dose!

$^{10}B[n,\alpha]^{7}Li$ reaction





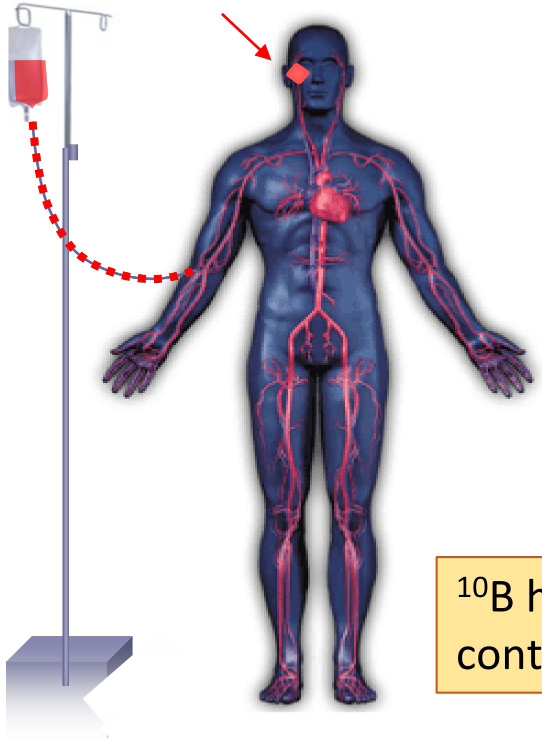
Boron loading : 20-50 µg/g ^{10}B

Main development in the last 20 years:

to find the optimal boron vector

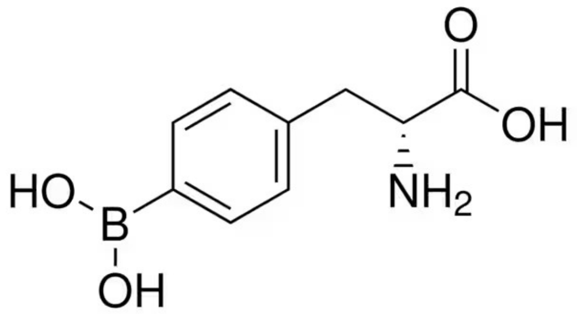
Tumor/blood ^{10}B ratio (1.5 – 5.0)

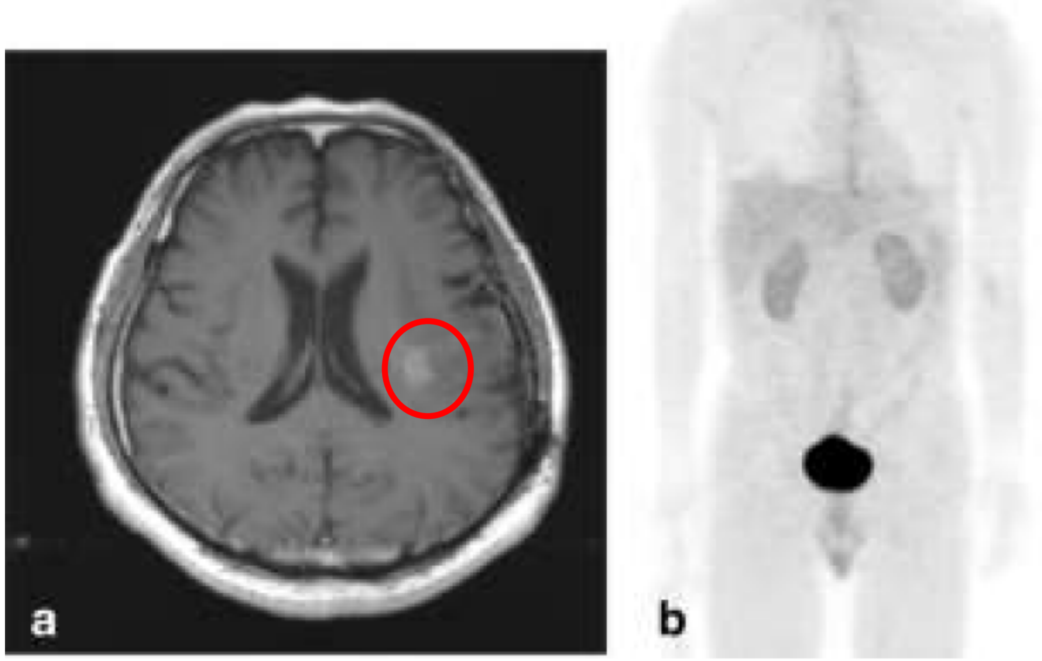
Tumor/normal tissue ^{10}B ratio



^{10}B human body content: 0,14 µg/g

4-BORONO-L-PHENYLALANINE (BPA for friends)



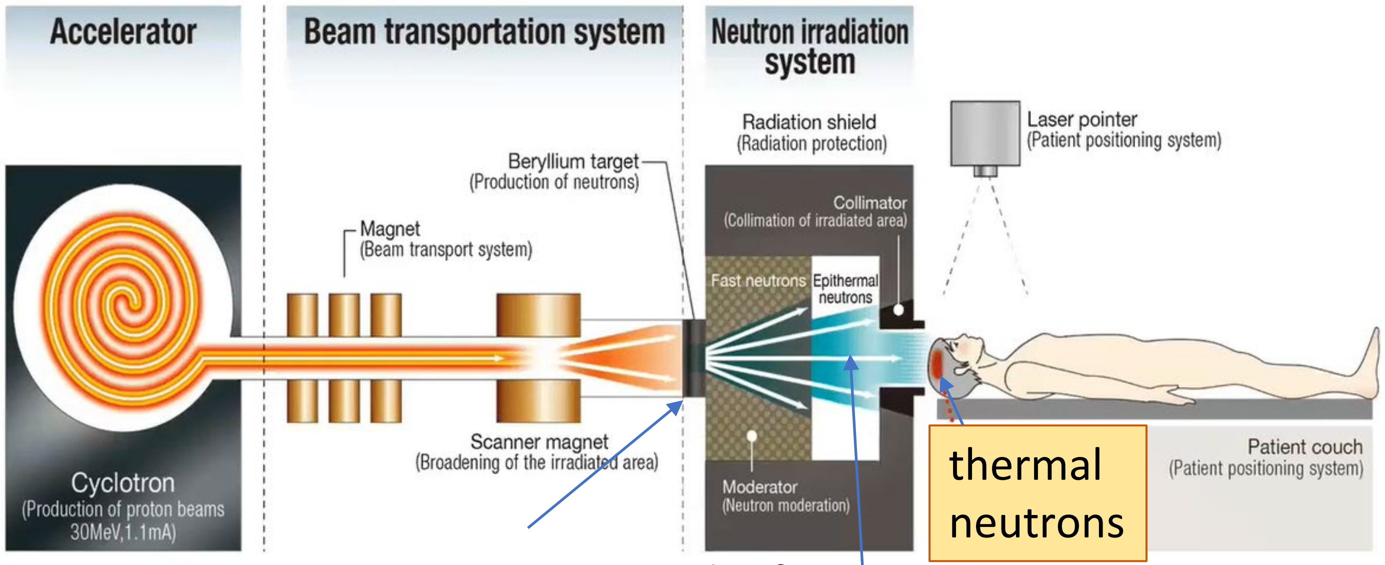


Which neutrons ?

First tests with thermal neutrons from reactors: difficult control

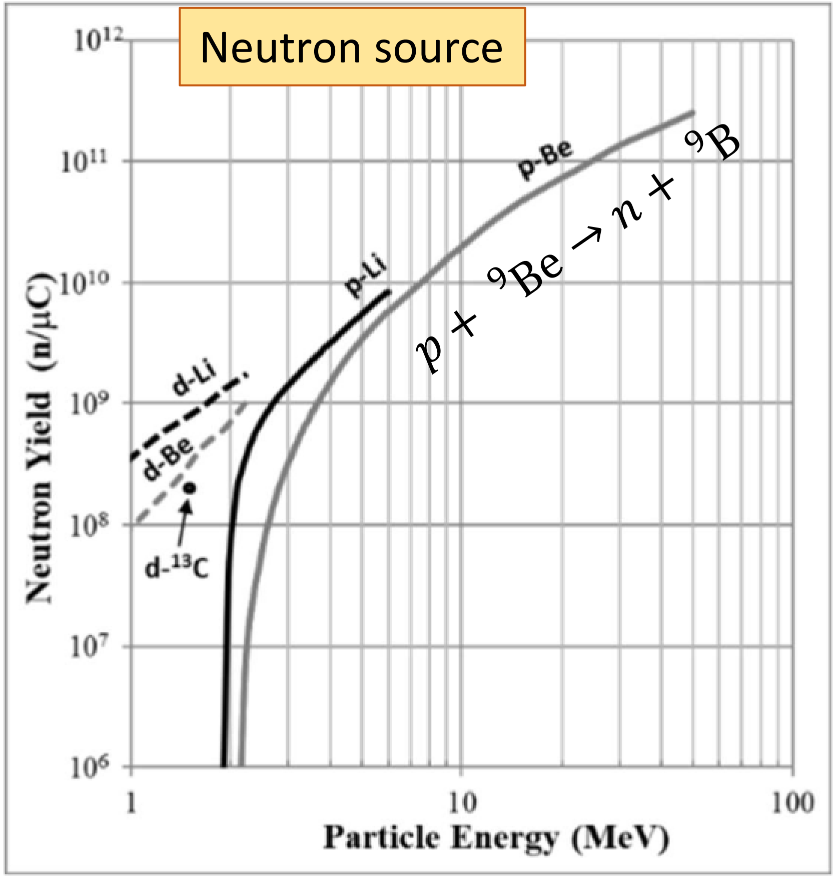
Now BNCT is done with the help of ion accelerators: much better control

Therapeutic fluence $\phi \approx 10^{12}$ n/cm^2



Be target: O(700) W/cm^2
Fast neutrons

Epithermal
neutrons



BNCT Facilities

IAEA

Total BNCT Facilities: 33

Total Countries: 13

Linac	Electrostatic	Cyclotron	Reactor
8	13	5	7

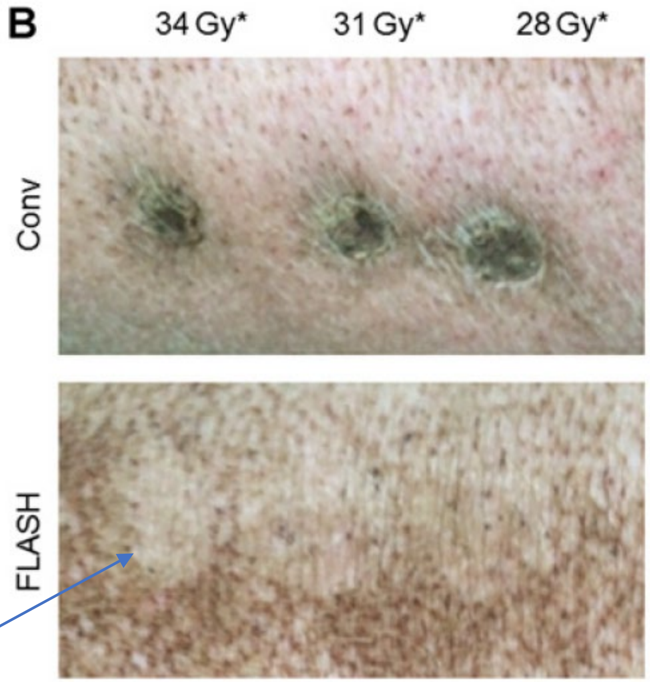
Reactor/Accelerator: All

Argentina	3
Belgium	1
China	5
Finland	1
Israel	1
Italy	3
Japan	10
Russia	2
South Korea	2
Spain	1
Taiwan, China	1
Thailand	1
United Kingdom	2

The FLASH effect and FLASH therapy

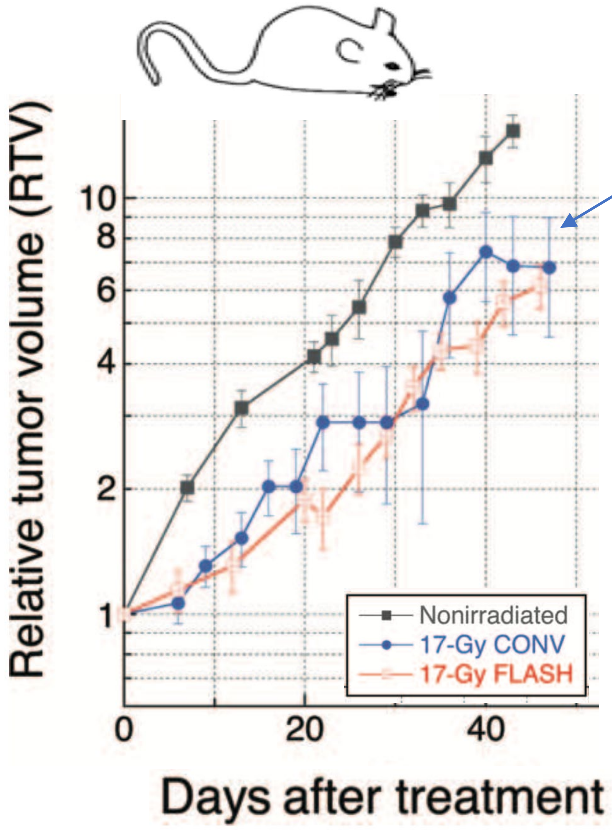
It has been discovered that the **irradiation rate** has an effect on cell survival probability
Conventional: 2 Gy delivered in minutes
Flash: 2 Gy delivered in milliseconds or microseconds

Initially healty pig skin



Minimal visible damage

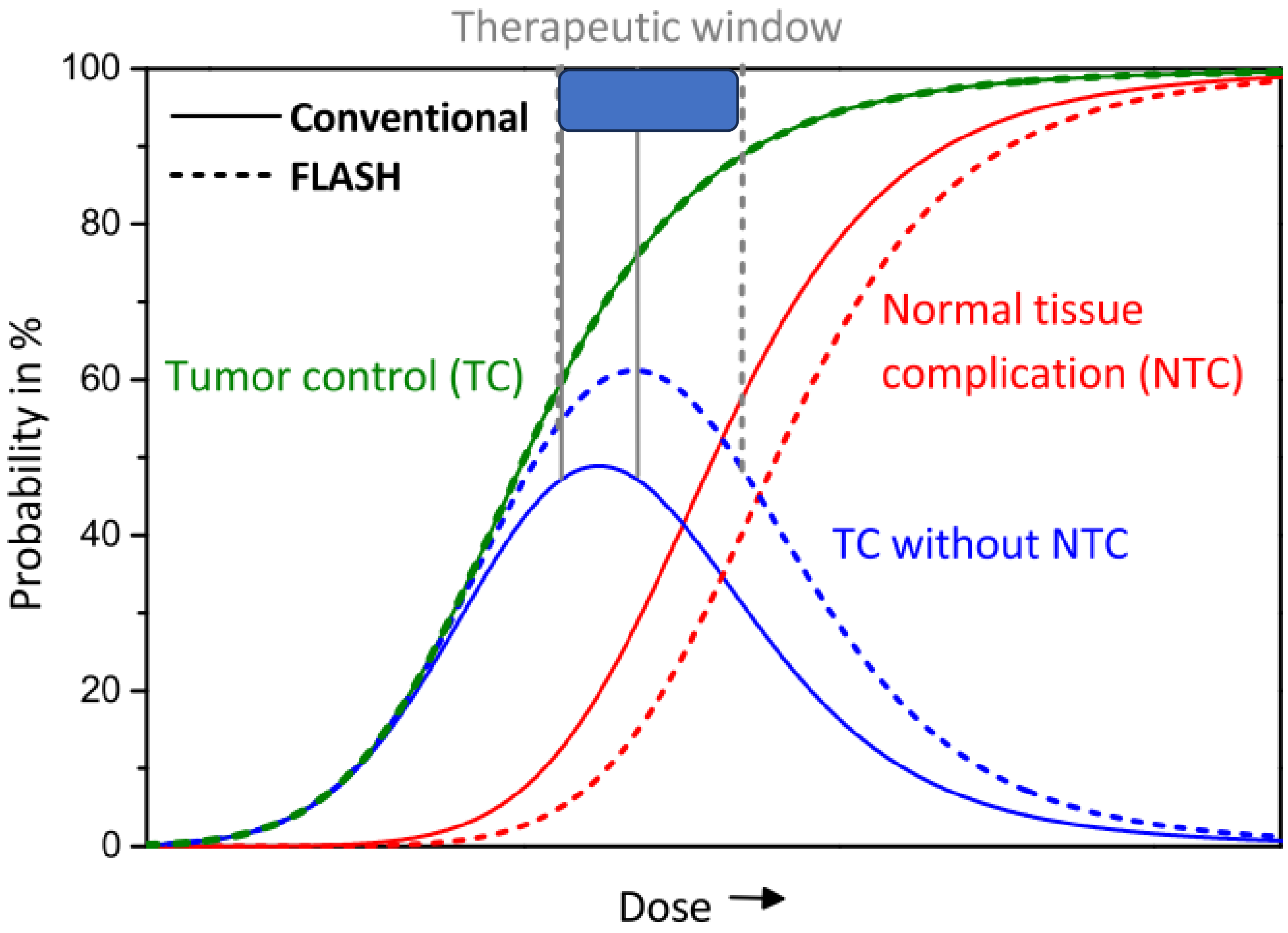
(Vozenin et al. 2019, Clin. Canc. Res.)



Flash therapy as good as conventional therapy on cancer cells

(V. Favaudon et al. 2014, Sci. Transl. Med.)

Enlarged therapeutic window

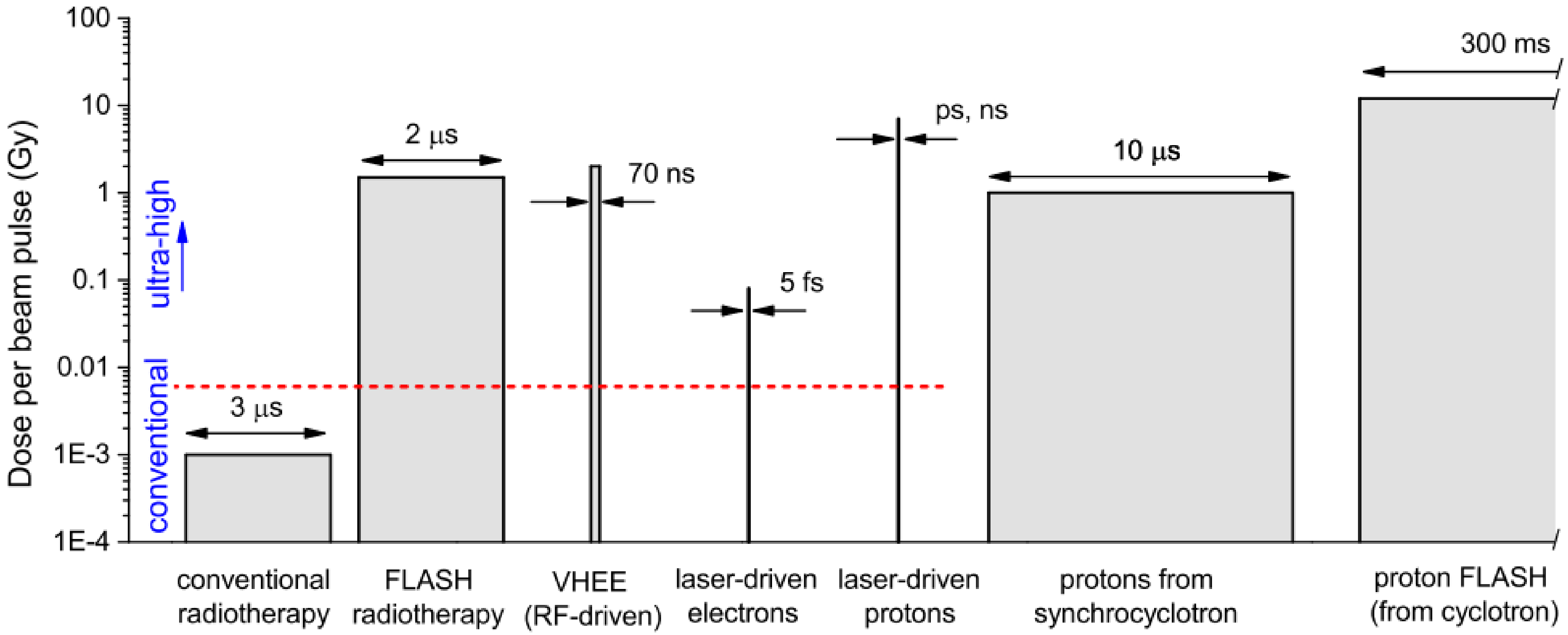


Advantages (choose one only):

- lower number of treatments (increasing doses)
- lower complicances probabilities (same dose)
- treatment of moving tumors (lung, abdomen)

Advances in accelerator technology

→ need **controlled** intensity pulses



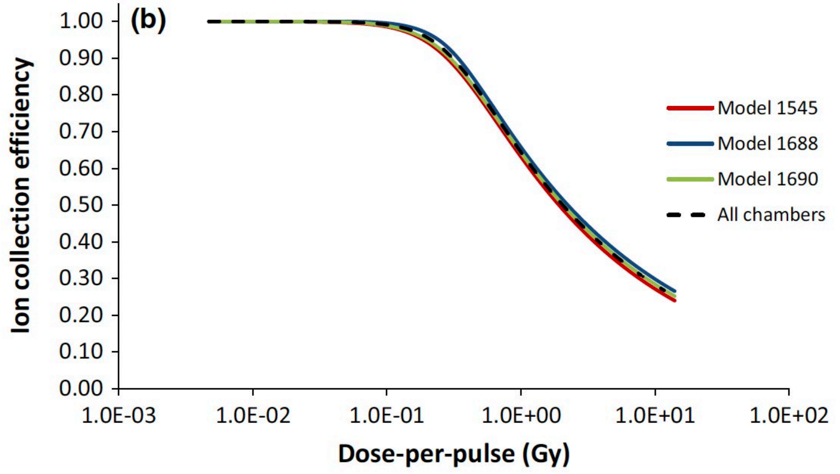
Dose monitoring

Dose monitoring is crucial. Current detectors do not fit the needs of FLASH therapy. Need to reach 200 Gy/s

→ Accuracy needed better than 3%

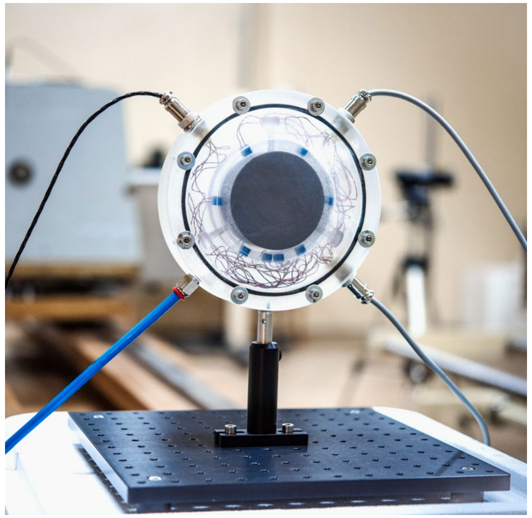
→ advances in the detector technology

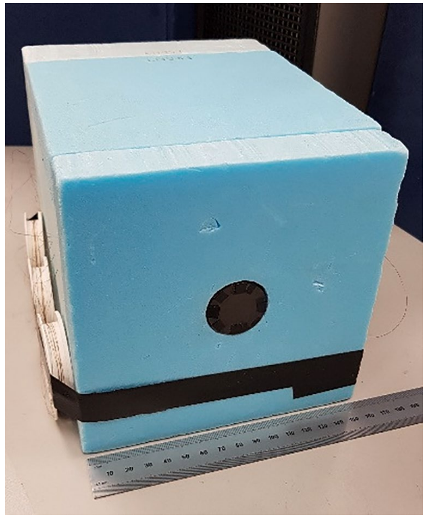
Ion chamber (for e and ion therapies)

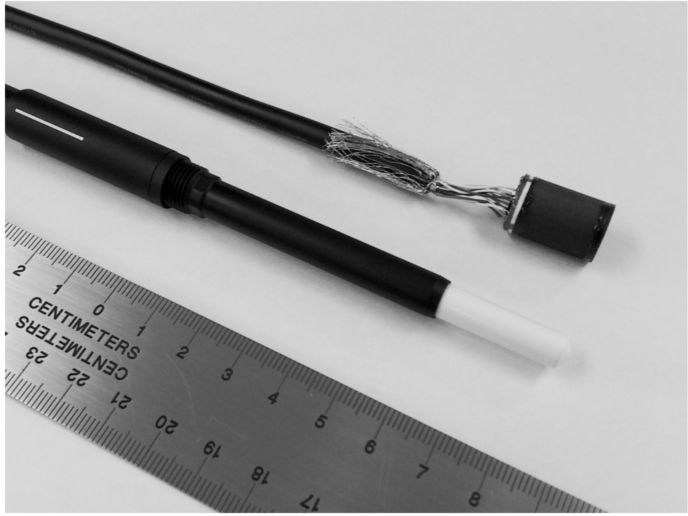


New detectors under study

(A. Shuller et al, Physica Medica 80 (2020) 134–150)







Redundancy needed for clinical practice!

Flash effect observed! Is it understood ?

NOT REALLY!

‘in-vitro’ studies can help **explaining** the effect?

What is the root source of such sparing? **Oxygen** could be involved but not in an easy/trivial way..

The assessment of this ‘new’ approach potential requires, now, answering many open questions..

Which physical processes helps in sparing healthy tissues ?

A **threshold effect** seems to be present.. The FLASH effect ‘kicks in’ only when the overall dose exceeds a certain **threshold**.. **Why?**

In medicine you can use a treatment if proven to be effective; no necessity to understand all the tiniest details!

Summary

Hadrontherapy is a stable clinical practice

and a very interesting field of research for different communities (FIS, BIO, MED)

We're doing at the same time:

- fundamental research
- applied research
- and trying to bring positive effects to the society

Thanks for the attention

Credits for slides, images and data

R. Spighi, M. Franchini, V. Patera, A. Sarti, G. Bisogni, G. Battistoni, M. Pullia, M. Necchi, S. Rossi, A. Pella, M. Colonna, S. Lorentini, and many others!

Bibliography

[1] H. Sung et al, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries", CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660.

[2] WD Newhouser and R. Zhang, “The physics of proton therapy”, Phys Med Biol. 2015 Apr 21; 60(8): R155–R209. doi: 10.1088/0031-9155/60/8/R155