

Seminar on HADRONTHERAPY

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OUTLINE

PART 1: Physics and radiobiology

- ***Physical basis of hadrontherapy***
 - Conformity of irradiation
 - Microscopic dose distribution in radiation therapy
- ***Biological effects***
 - Cell survival and fractionation
 - RadioBiological Effectiveness (RBE)

PART 2: Accelerators and technology

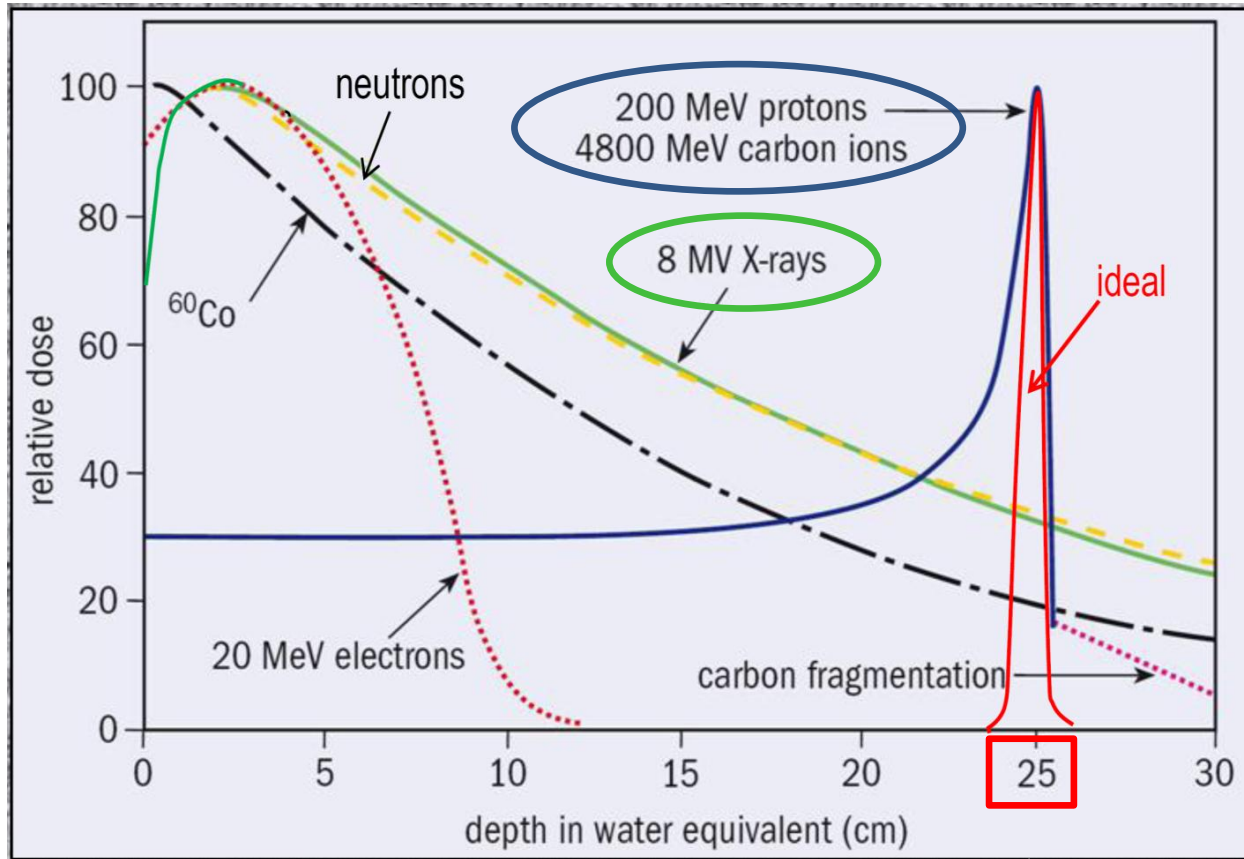
- ***Instrumentation and treatment modalities***
 - Accelerators for hadrontherapy
 - Active and passive scanning
- ***Future challenges in hadrontherapy (treatments and technologies)***
 - Moving organs
 - Single room facilities and gantries

CONCLUSION

Part 1: Physics and radiobiology

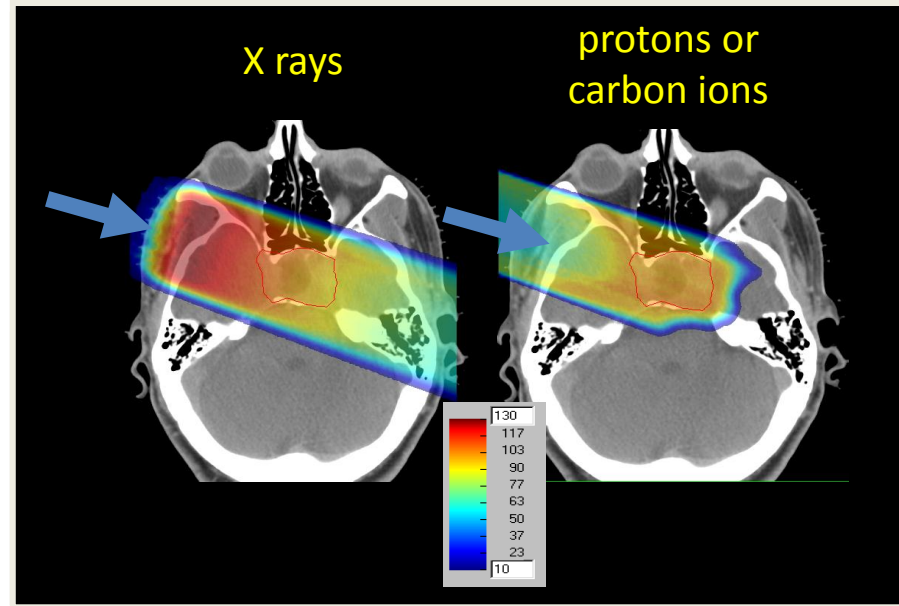
Physical basis of hadrontherapy

The icon of radiation therapy with charged hadrons



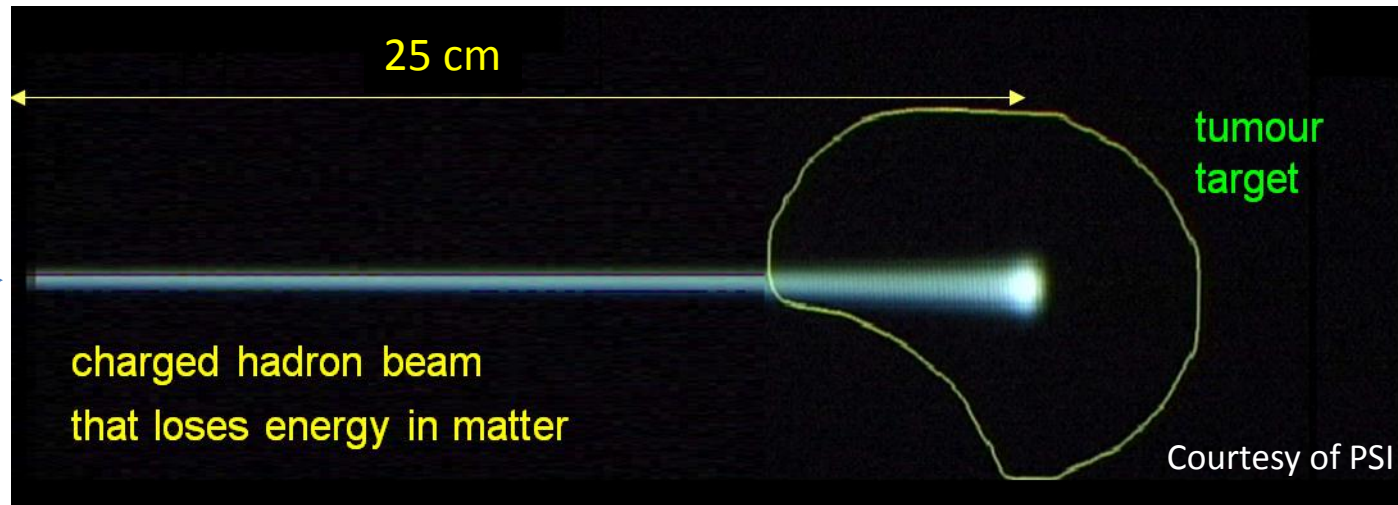
Radiation beam in matter

Protons and ions spare healthy tissues

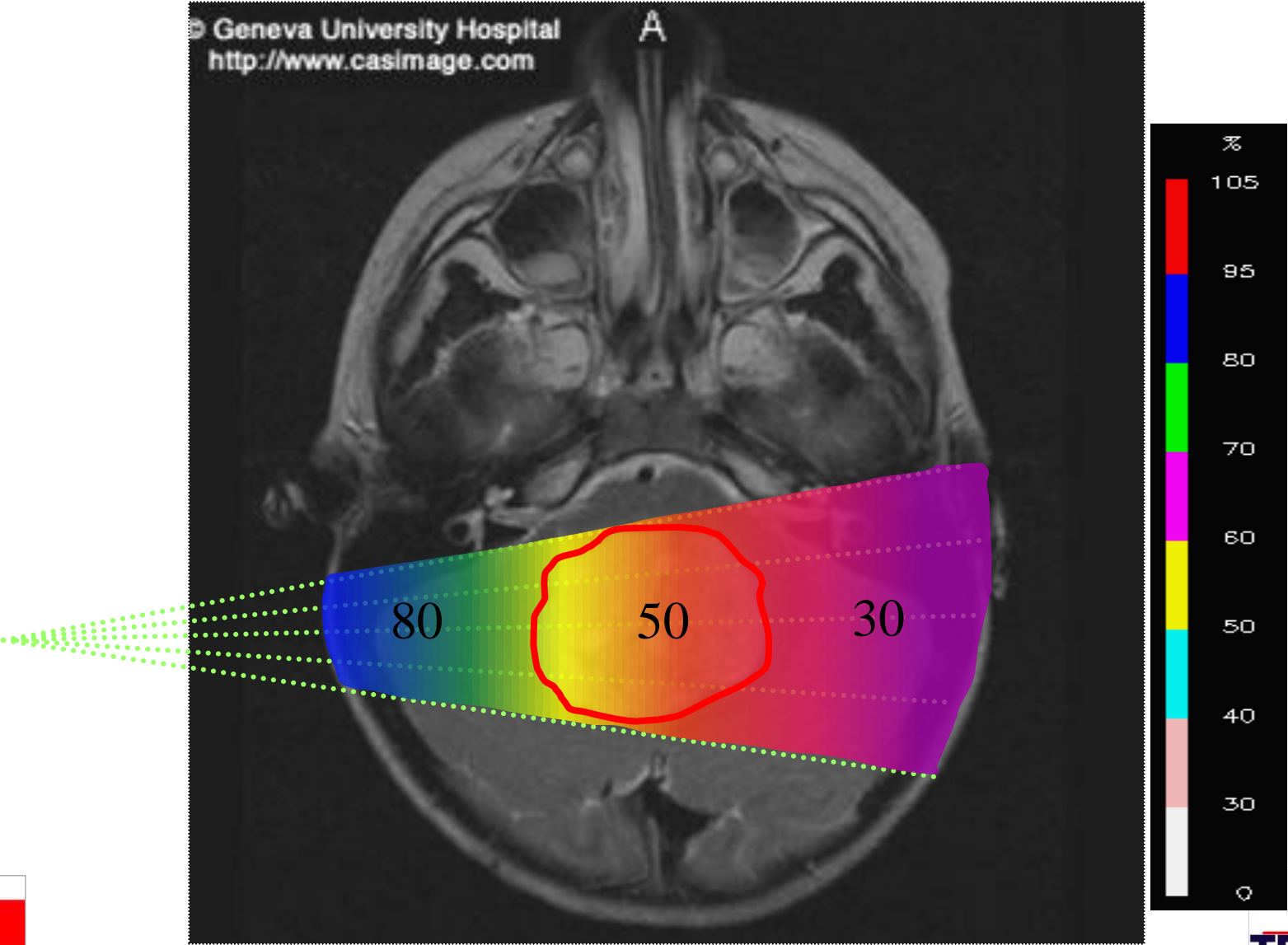


200 MeV - 1 nA
protons

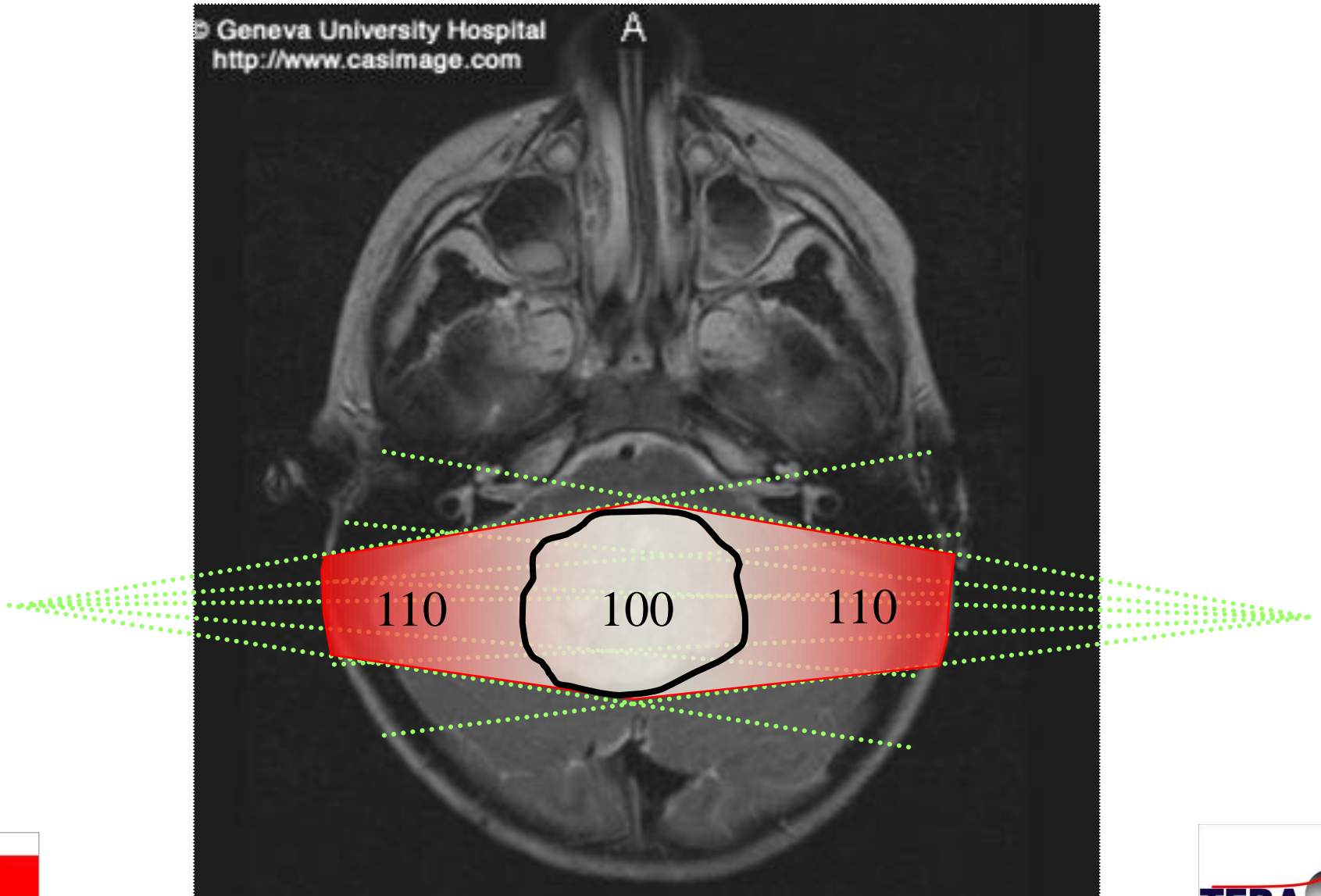
4800 MeV - 0.1 nA
carbon ions
(radioresistant tumours)



One lateral photon beam deliver a non conformal dose

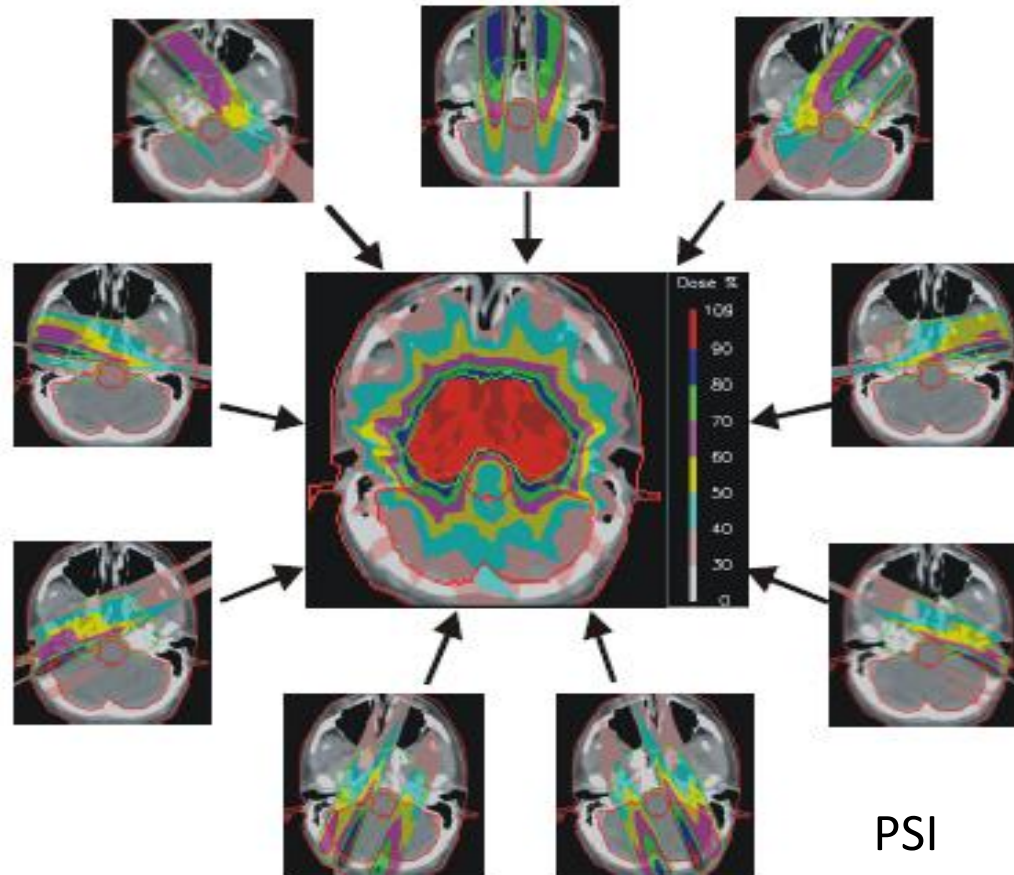


Two opposite photon beams are not enough to deliver a conformal dose



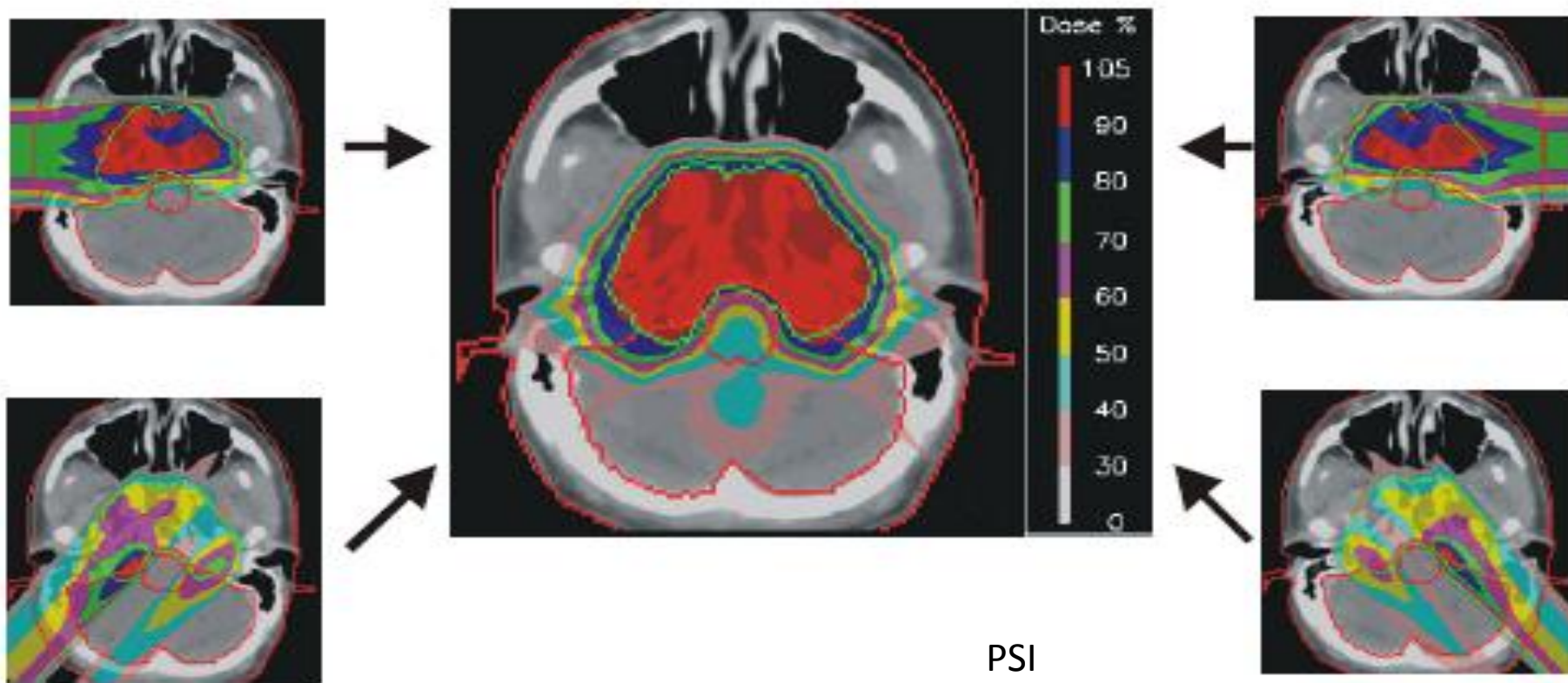
IMRT = Intensity Modulated Radiation Therapy with photons

9 NON-UNIFORM FIELDS

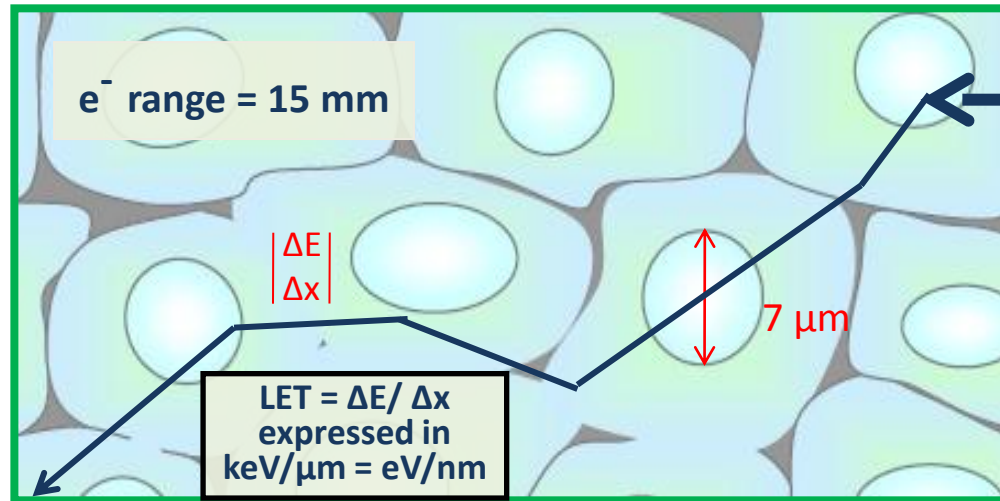
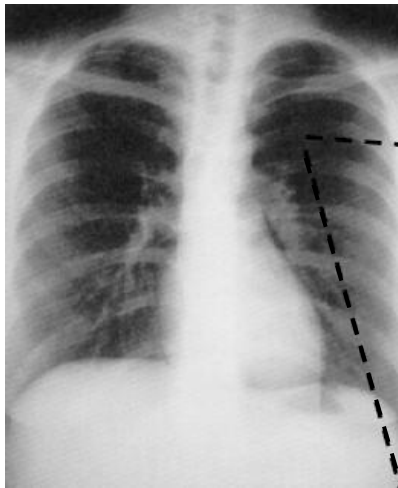


IMPT = Intensity Modulated Particle Therapy with protons

4 NON-UNIFORM FIELDS

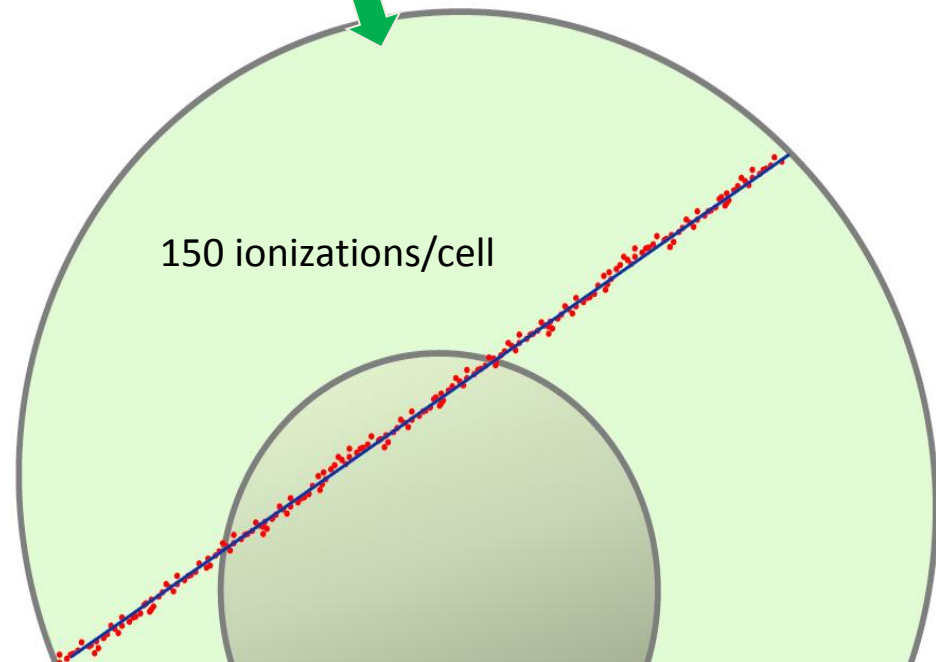
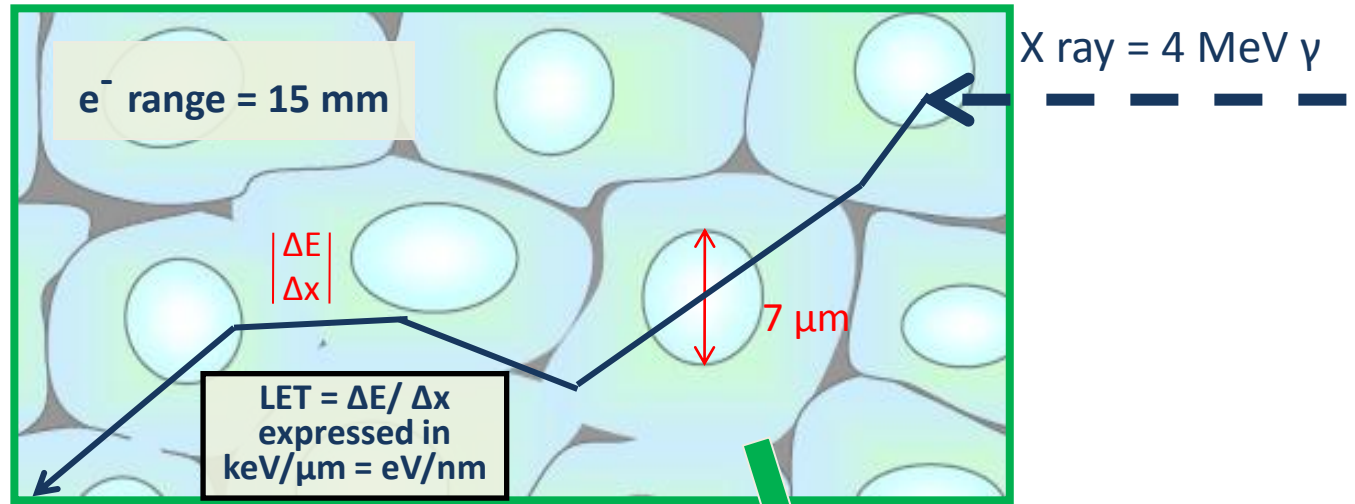
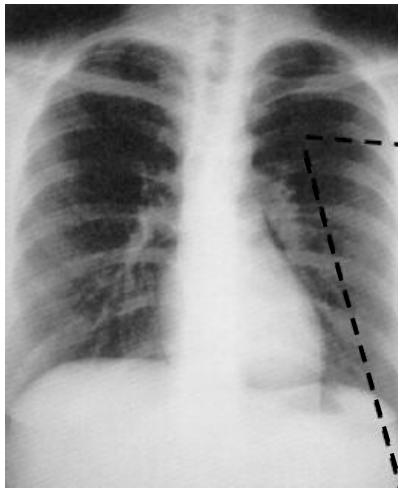


Microscopic distribution of the X-rays dose

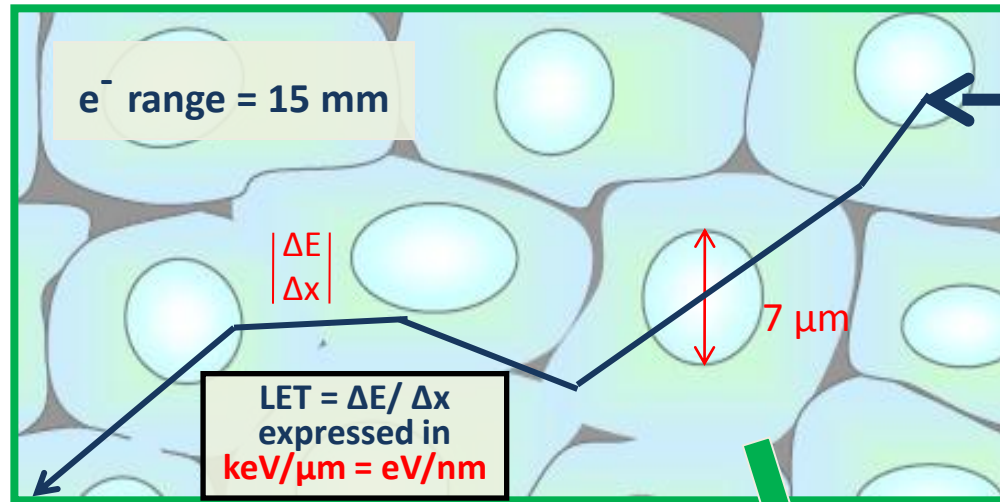
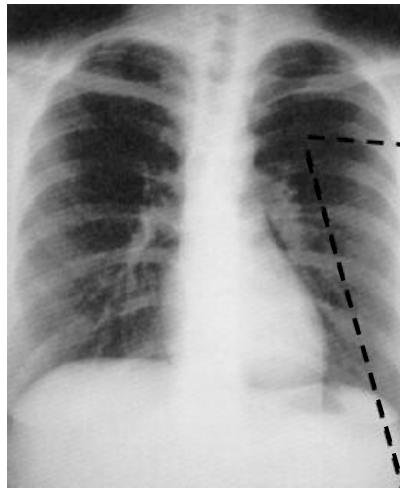


X ray = 4 MeV γ

Microscopic distribution of the X-rays dose

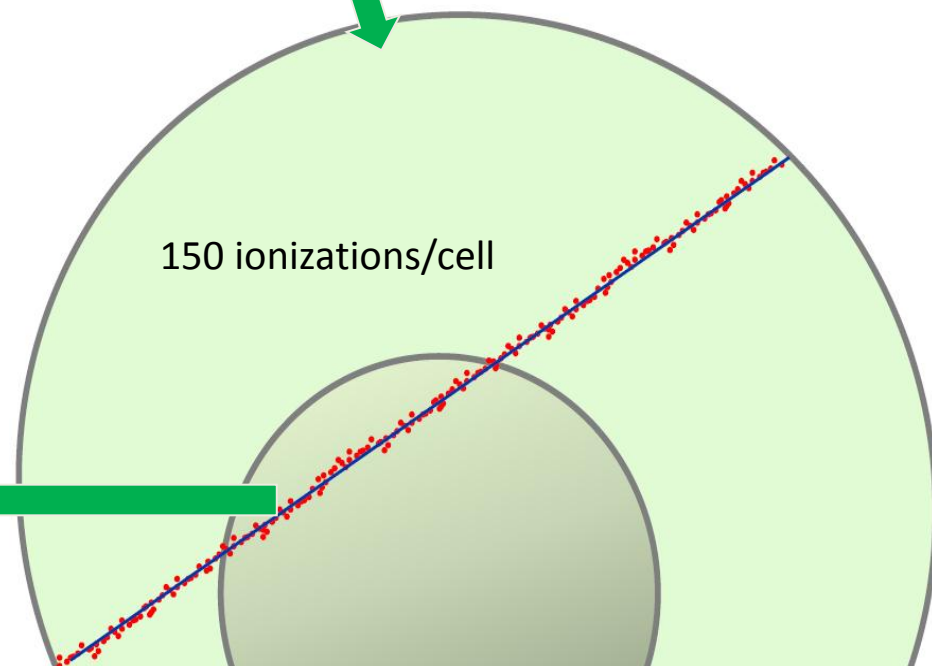
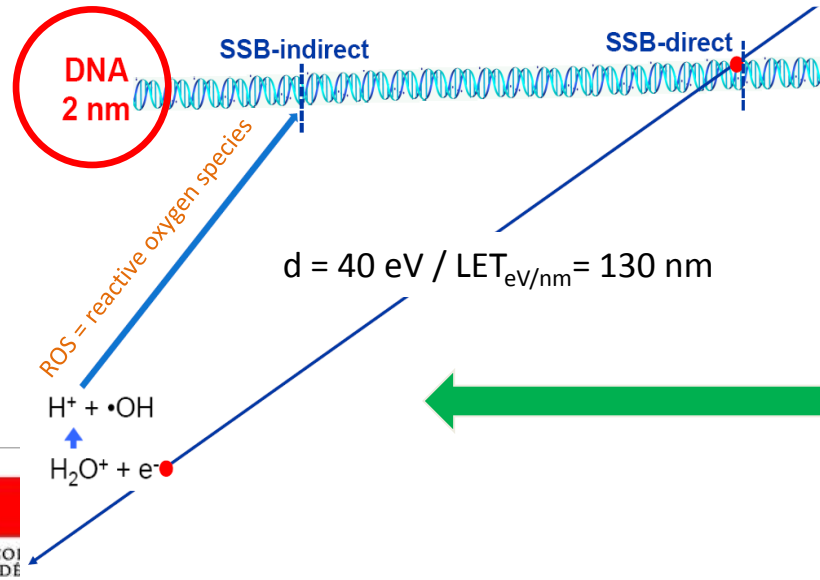


Microscopic distribution of the X-rays dose

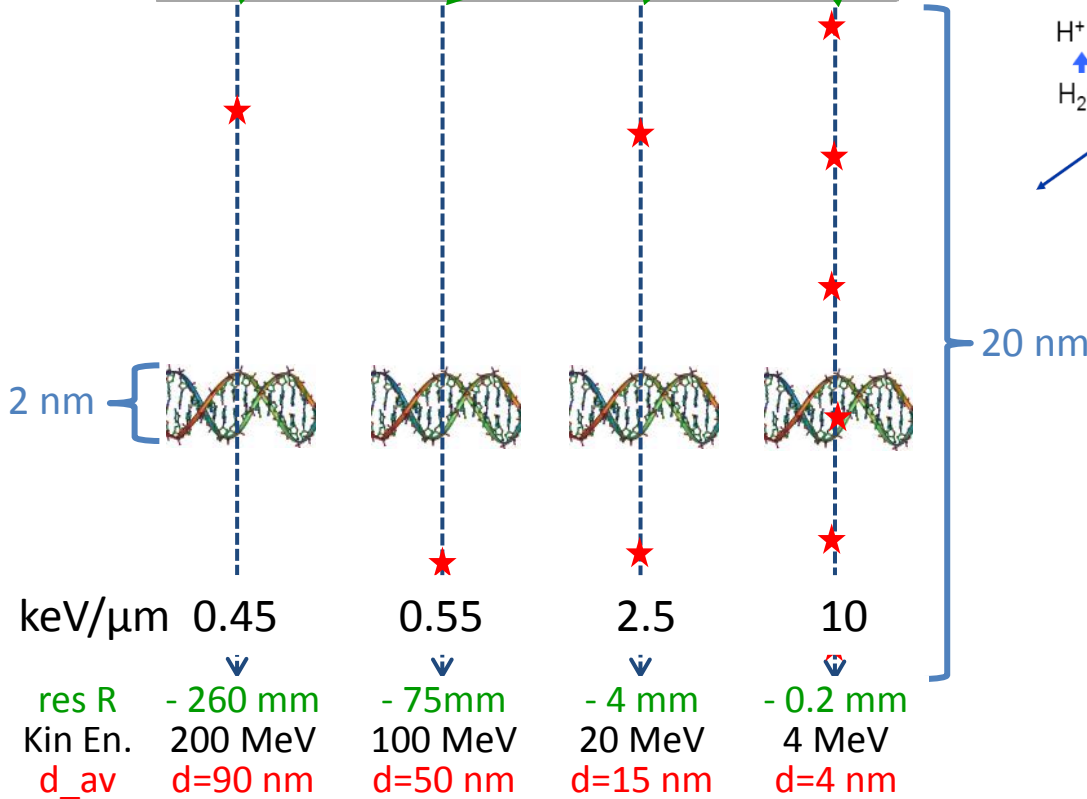
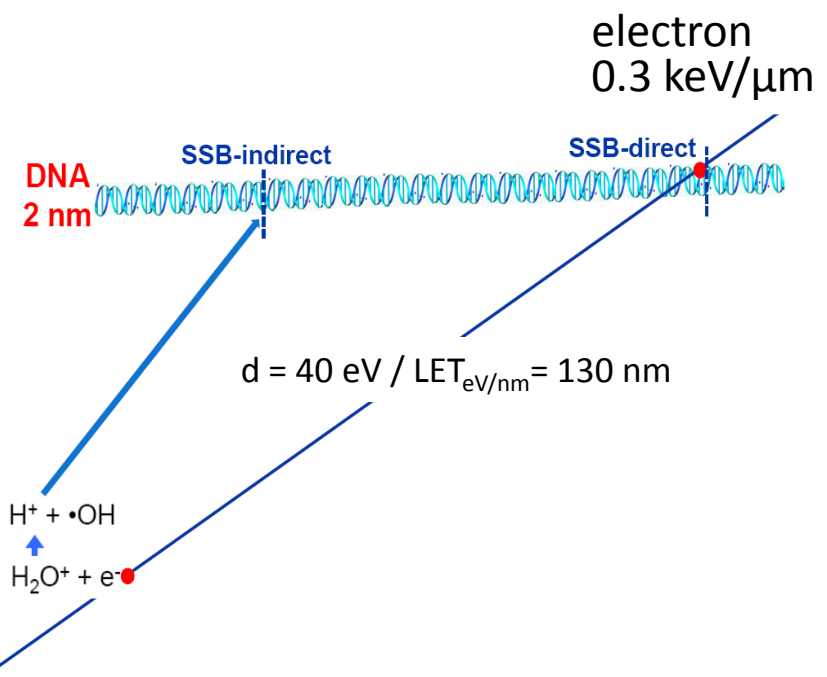
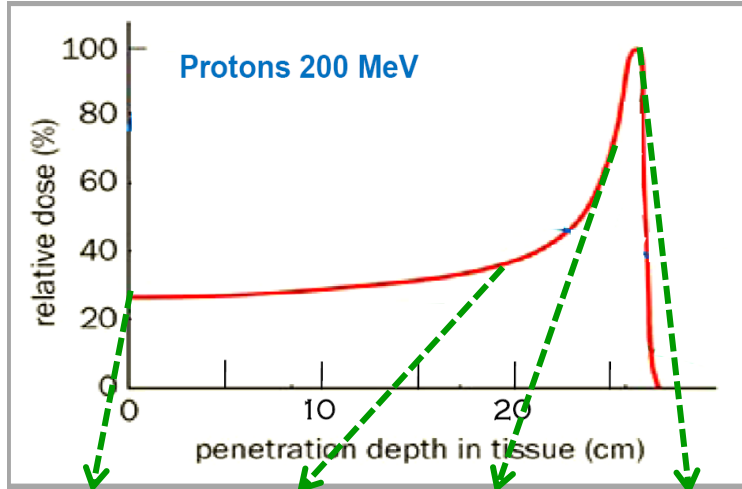


SSB =
Single Strand Break

electron
0.3 keV/ μm



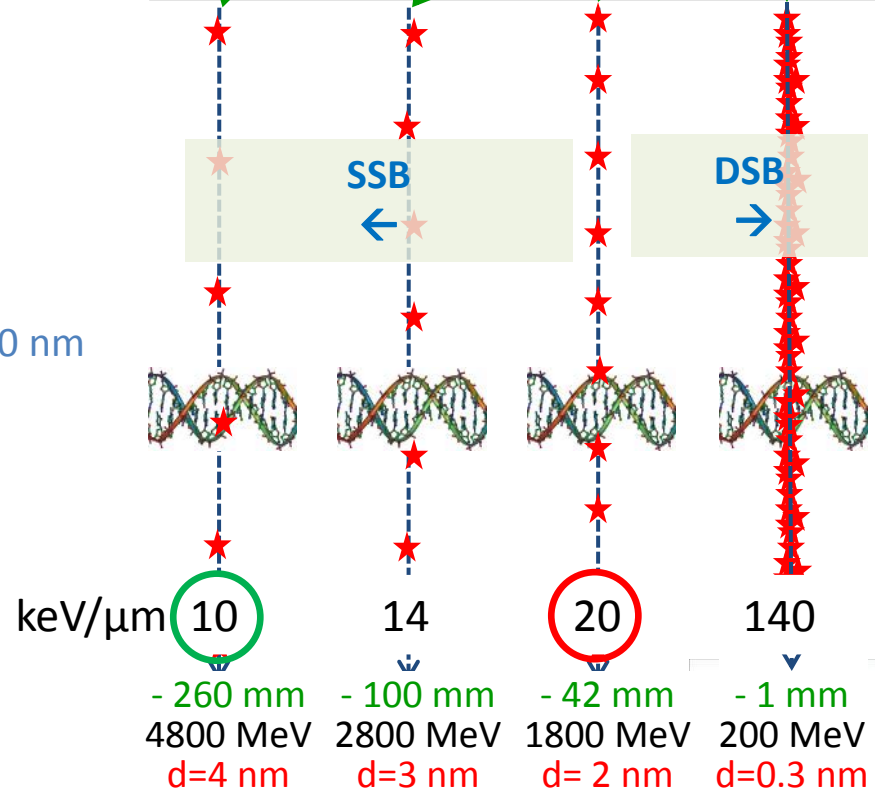
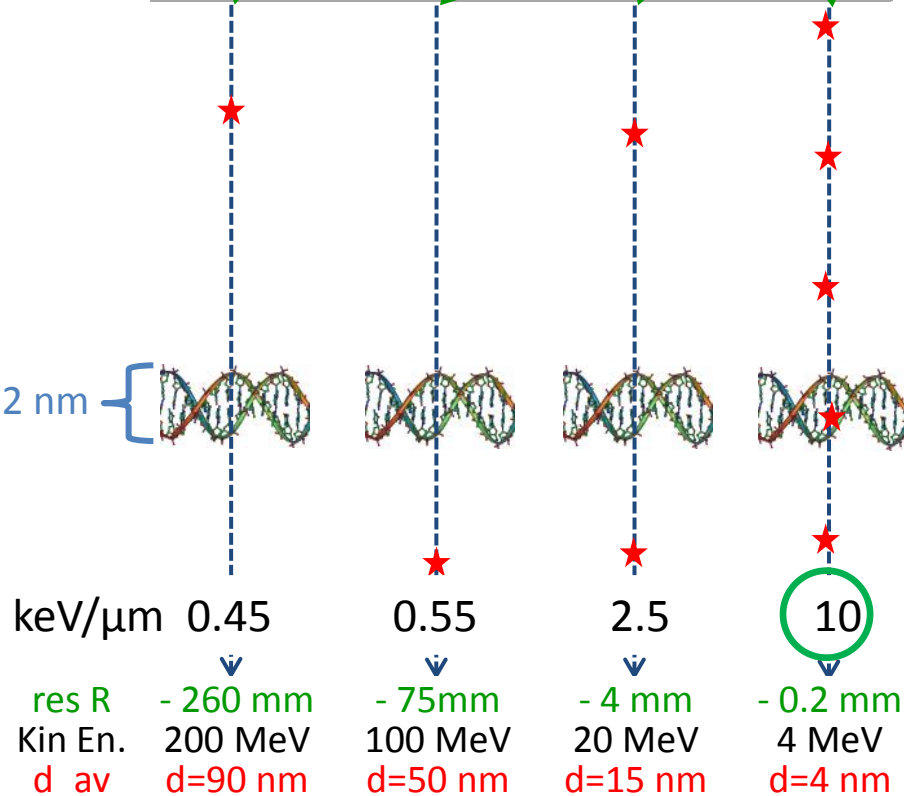
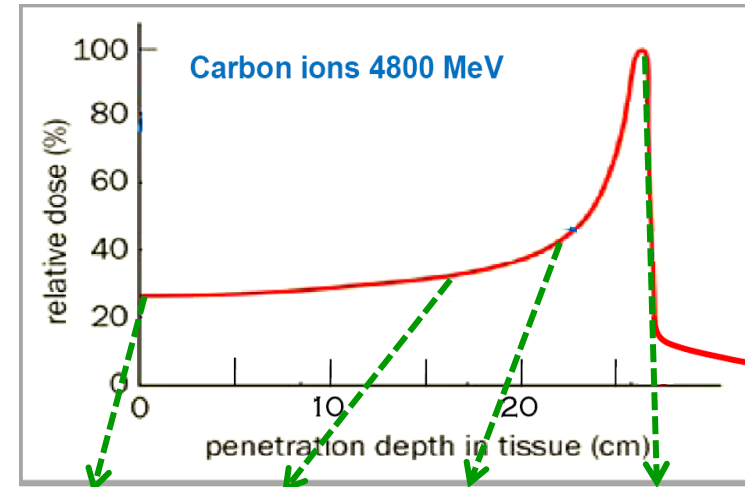
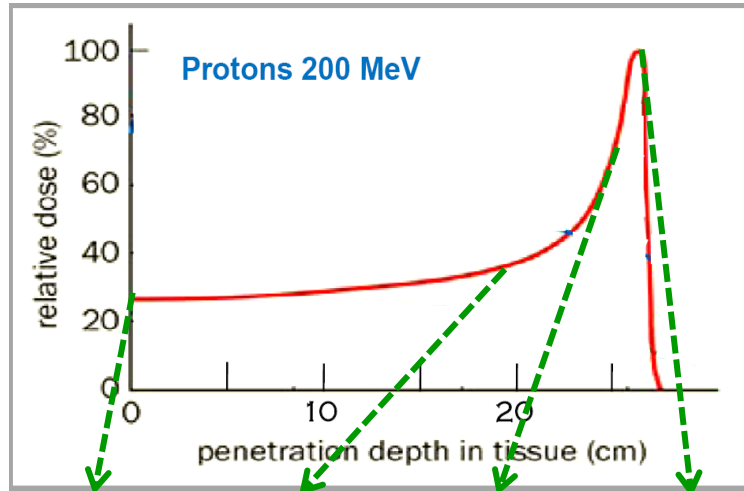
Microscopic distribution of the hadronic ionizations



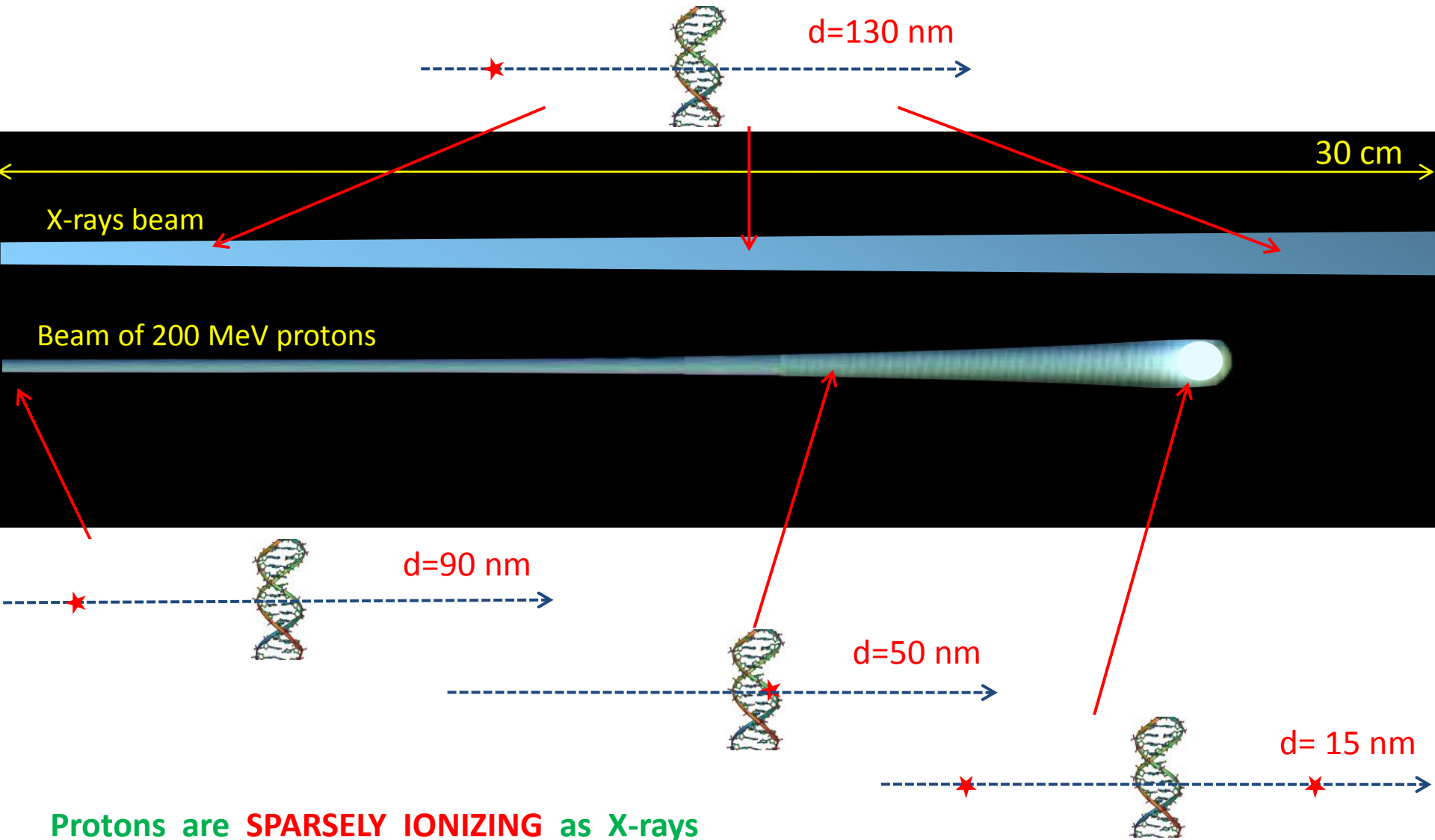
Protons are SPARSELY IONIZING

Protons are quantitatively different from X-rays

Microscopic distribution of the hadronic ionizations

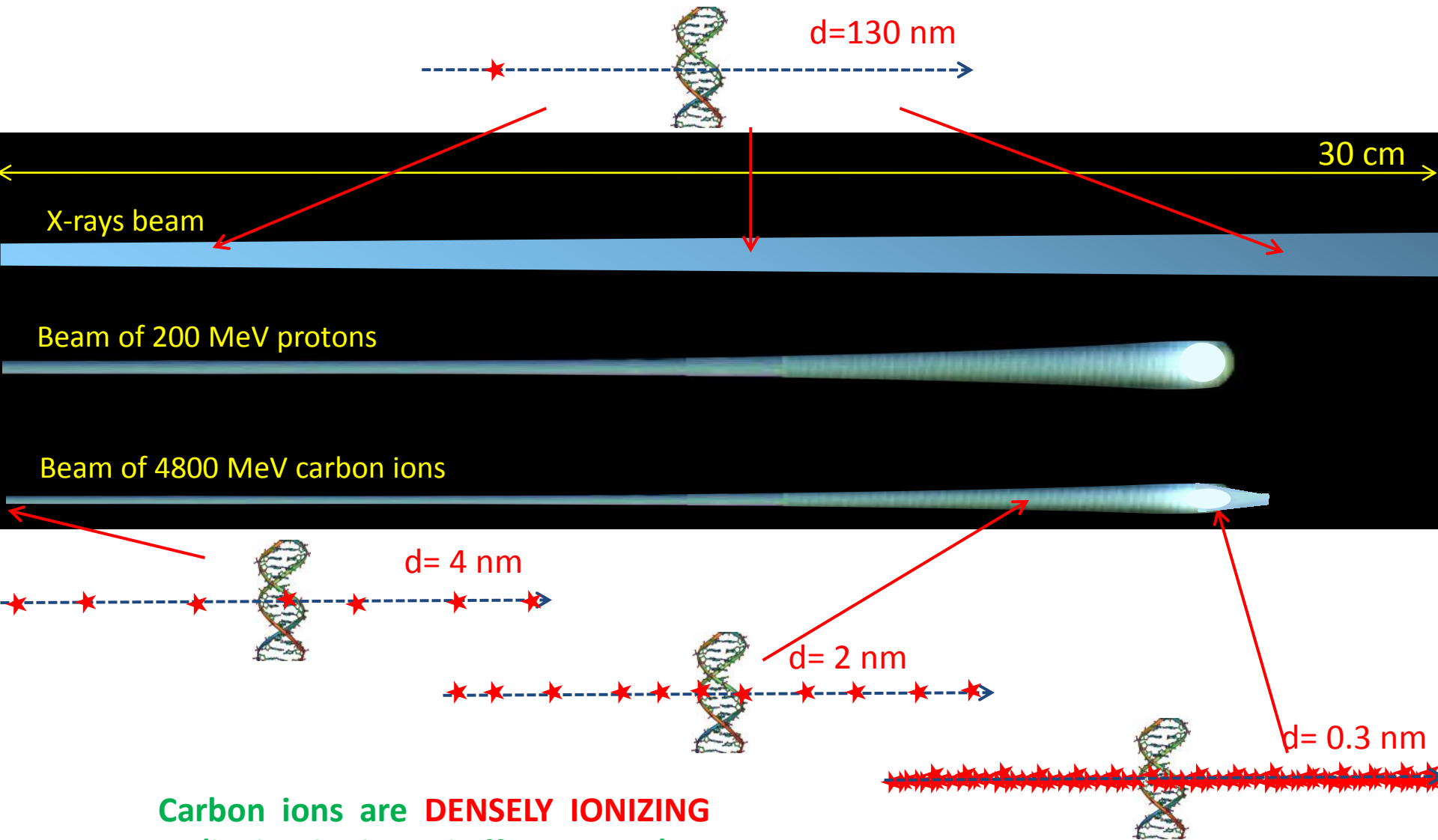


Protons: 1. more favorable dose 2. same 'indirect effects'



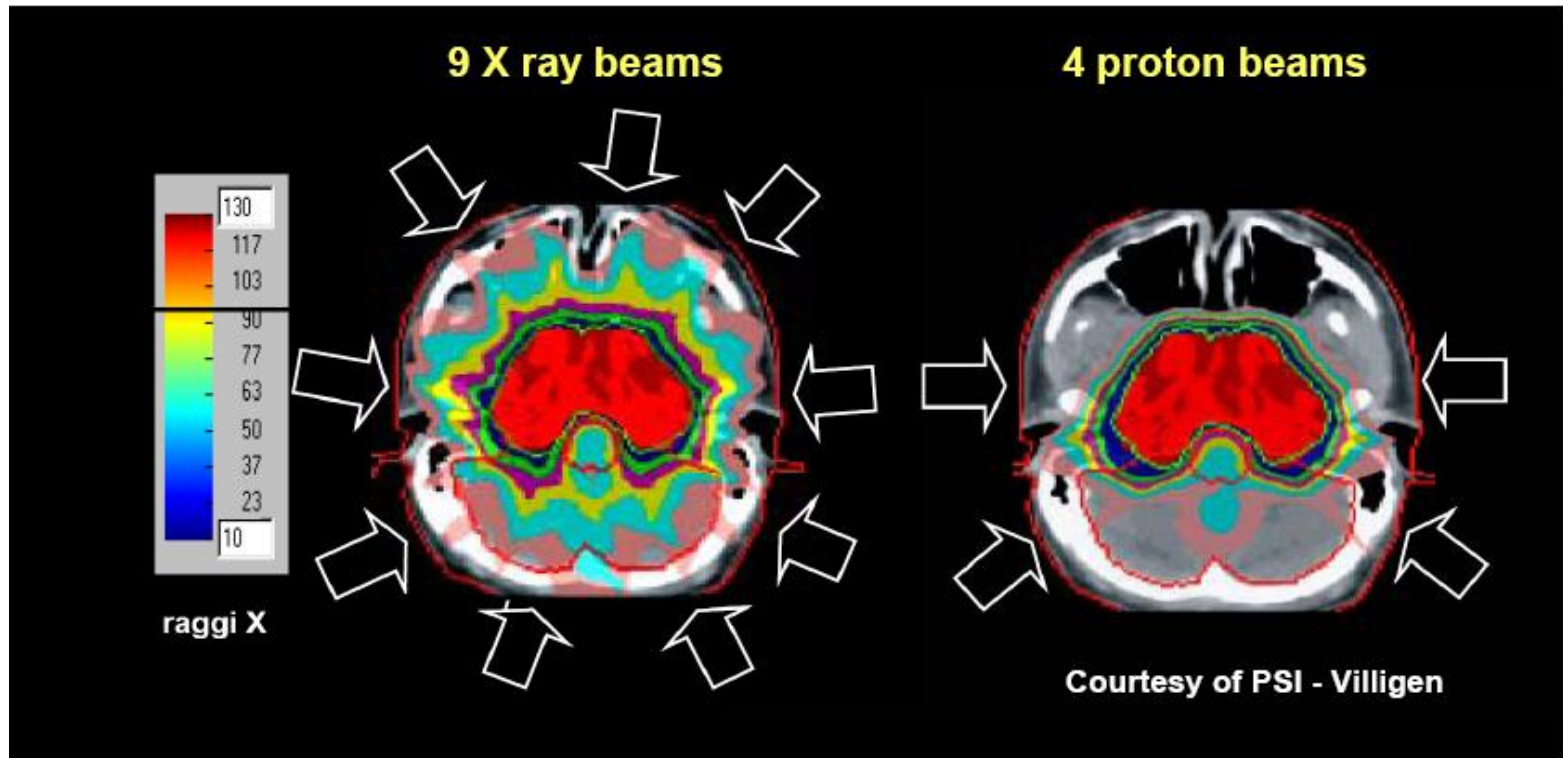
Protons are **SPARSELY IONIZING** as X-rays

Carbon ions: 1. more favorable dose 2. 'direct effects'



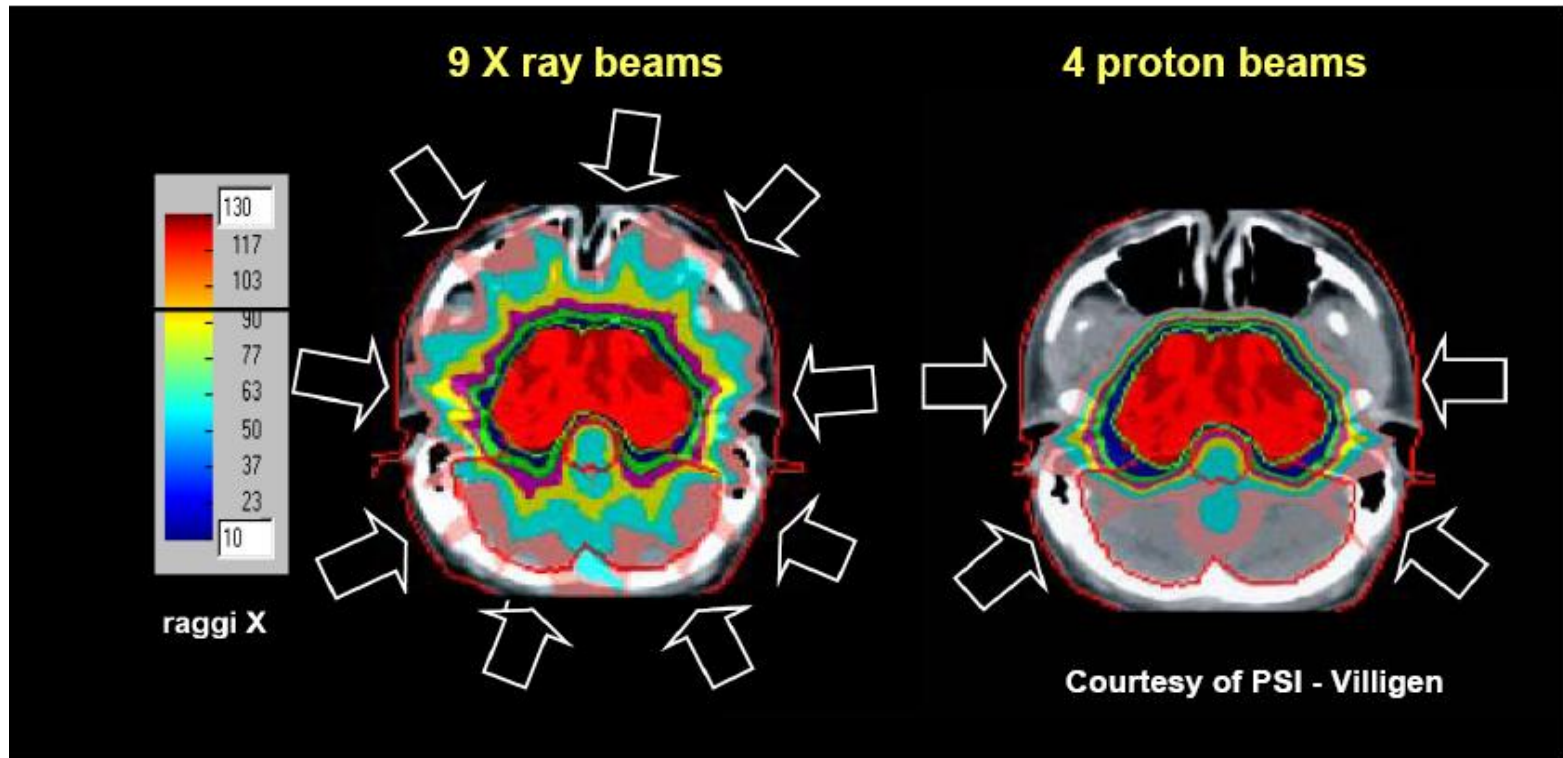
Carbon ions are **DENSELY IONIZING**
(higher biological effectiveness)

Protons are quantitatively different from X-rays



- The main difference is in the Bragg Peak.
- At the microscopic level both are **sparsely ionizing radiations**.

Carbon ions are qualitatively different from X-rays



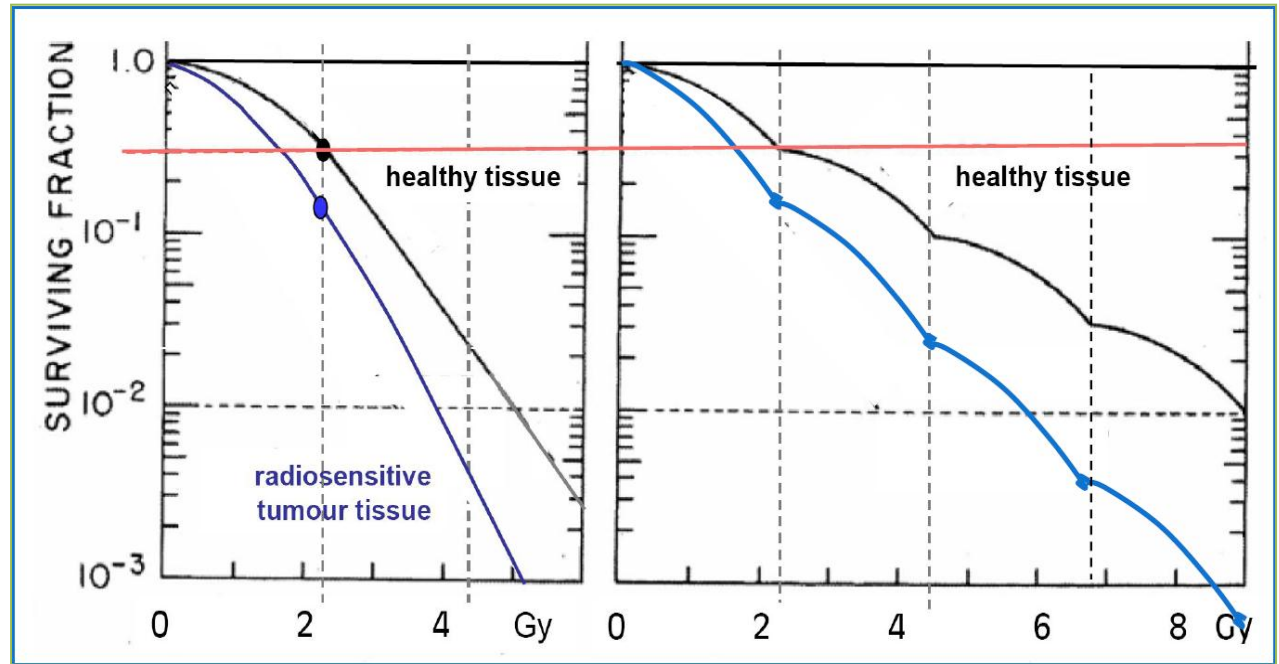
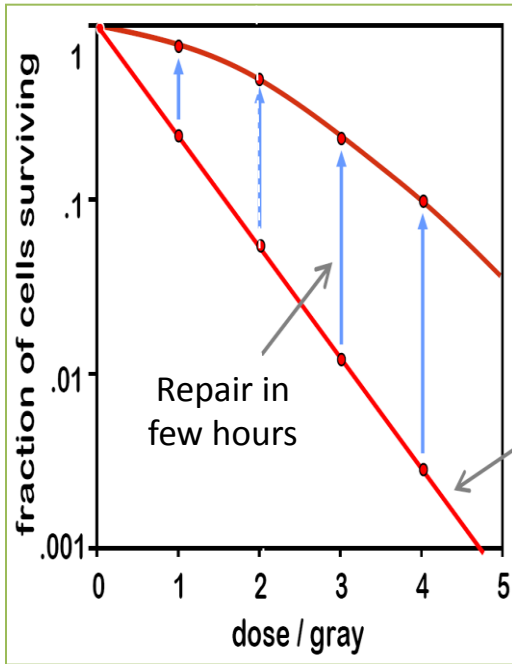
- Carbon ions deposit in a cell 22 times more energy than a proton producing not reparable **multiple close-by Double Strand Breaks**
- Carbon ions can control **radioresistant tumours**

Part 1: Physics and radiobiology

Biological effects

Cell survival and fractionation

For 80-90 % of the solid tumours, the tumour tissues are more 'radiosensitive' than healthy tissues



1 gray = 1 Gy = 1 J/kg

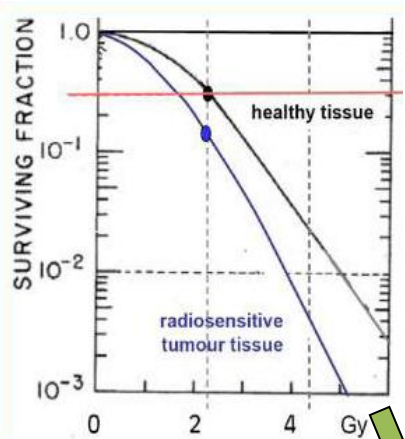
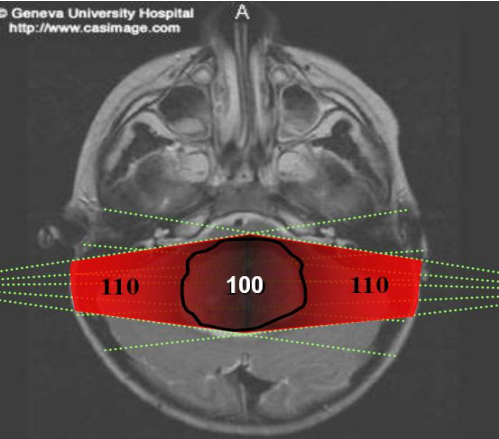
30 000 ionizations per nucleus

due to 200 electrons

60-75 Gy are typically given in 30 fractions over 6 weeks so that healthy tissues have the time to repair. Argument:

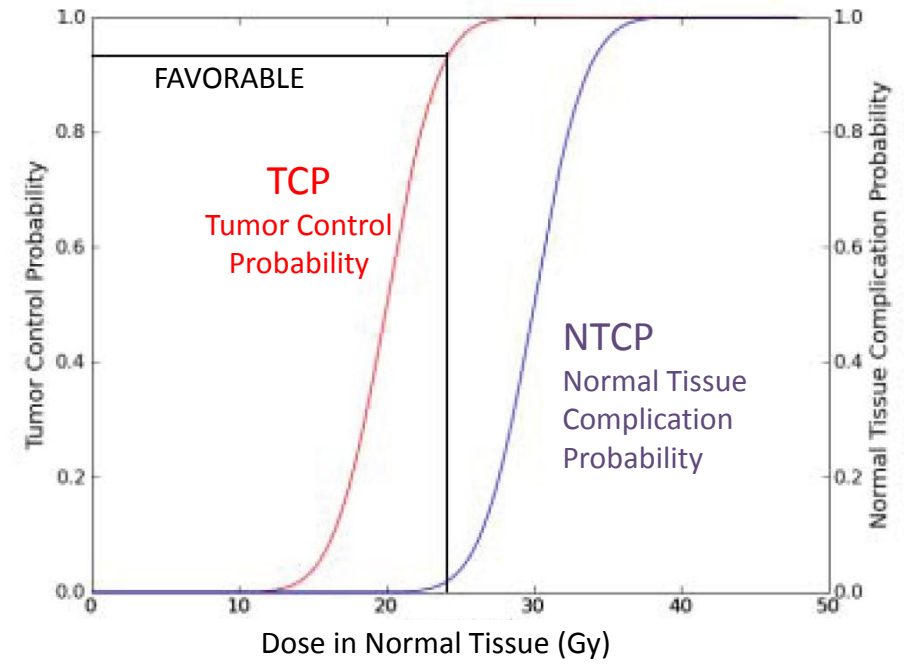
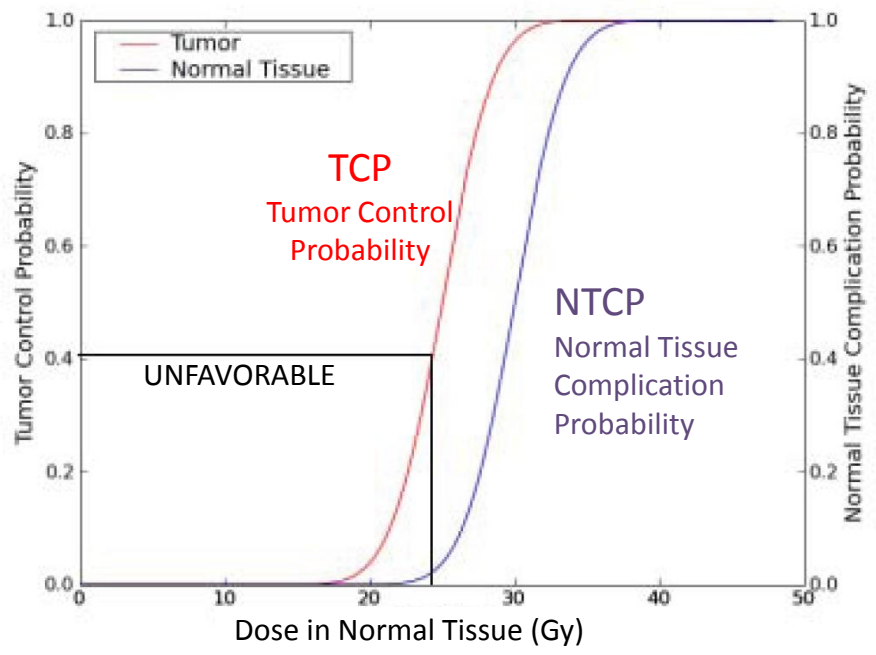
$(1/2)^{30} = 10^{-9}$ and there are 10^8 cells in 1 litre tumour

The tumour dose is limited by the nearby healthy tissues which cannot receive more than 30-40 Gy .



The therapeutic window

many biological and clinical phenomena in 30 sessions

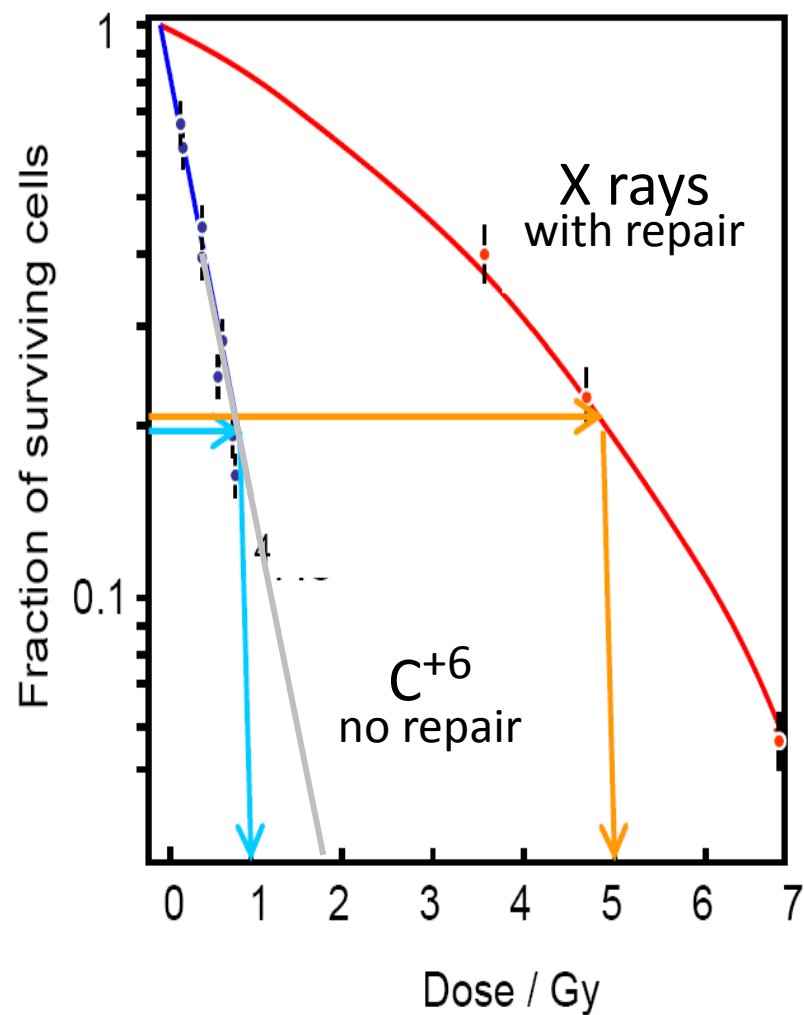


Definition of Radio-Biological Effectiveness (RBE)

RBE is defined with respect to standard X-rays:

$$RBE = \frac{D_{\gamma}}{D} = \frac{5}{1}$$

For a given effect on a given cell
the RBE value is a function of LET



Elective indications of carbon ions

Radioresistance
of the TUMOUR

radioresistant
tumour

radiosensitive
tumour

YES

YES

NO

YES

7%

3%

80%

10%

radioresistant
healthy tissue

radiosensitive
healthy tissue

Radioresistance
of the NORMAL
TISSUES

Numbers of potential patients (*)

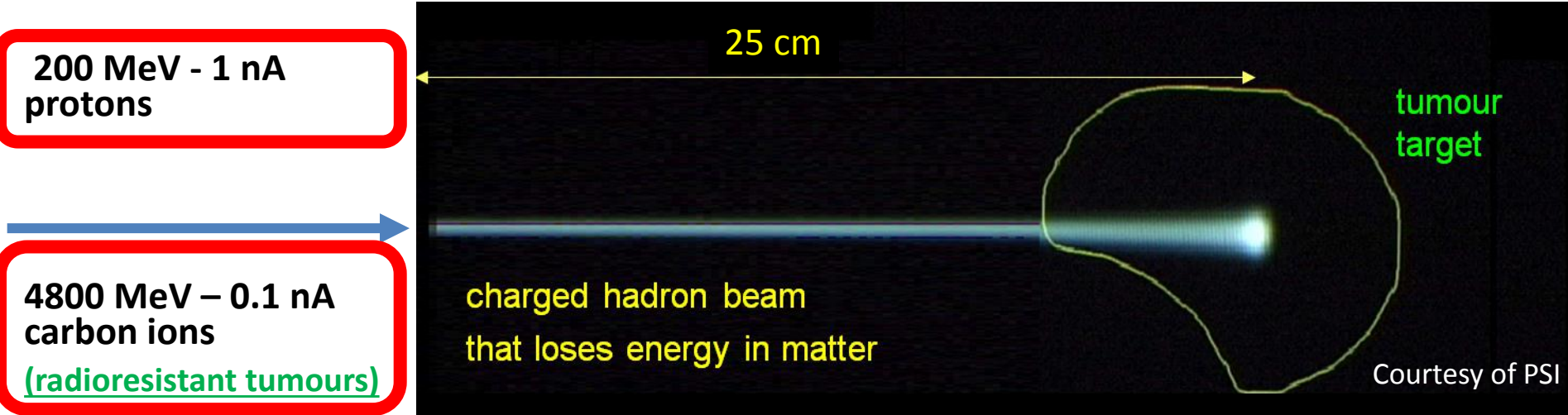
- X-ray therapy
every 10 million inhabitants: 20'000 pts/year
 - Protontherapy
12% of X-ray patients 2'400 pts/year
 - Therapy with Carbon ions for radio-resistant tumour
3% of X-ray patients 600 pts/year
- TOTAL every 10 M about 3'000 pts/year**

(*) Combining studies made in Austria, Germany, France and Italy in the framework of ENLIGHT - Coordinator: Manjit Dosanjh –

Projects in FP7: ULICE, PARTNER, ENVISION , ENTERVISION for a total of 22 MEuro

Summary 1st part

The basic principles of hadrontherapy

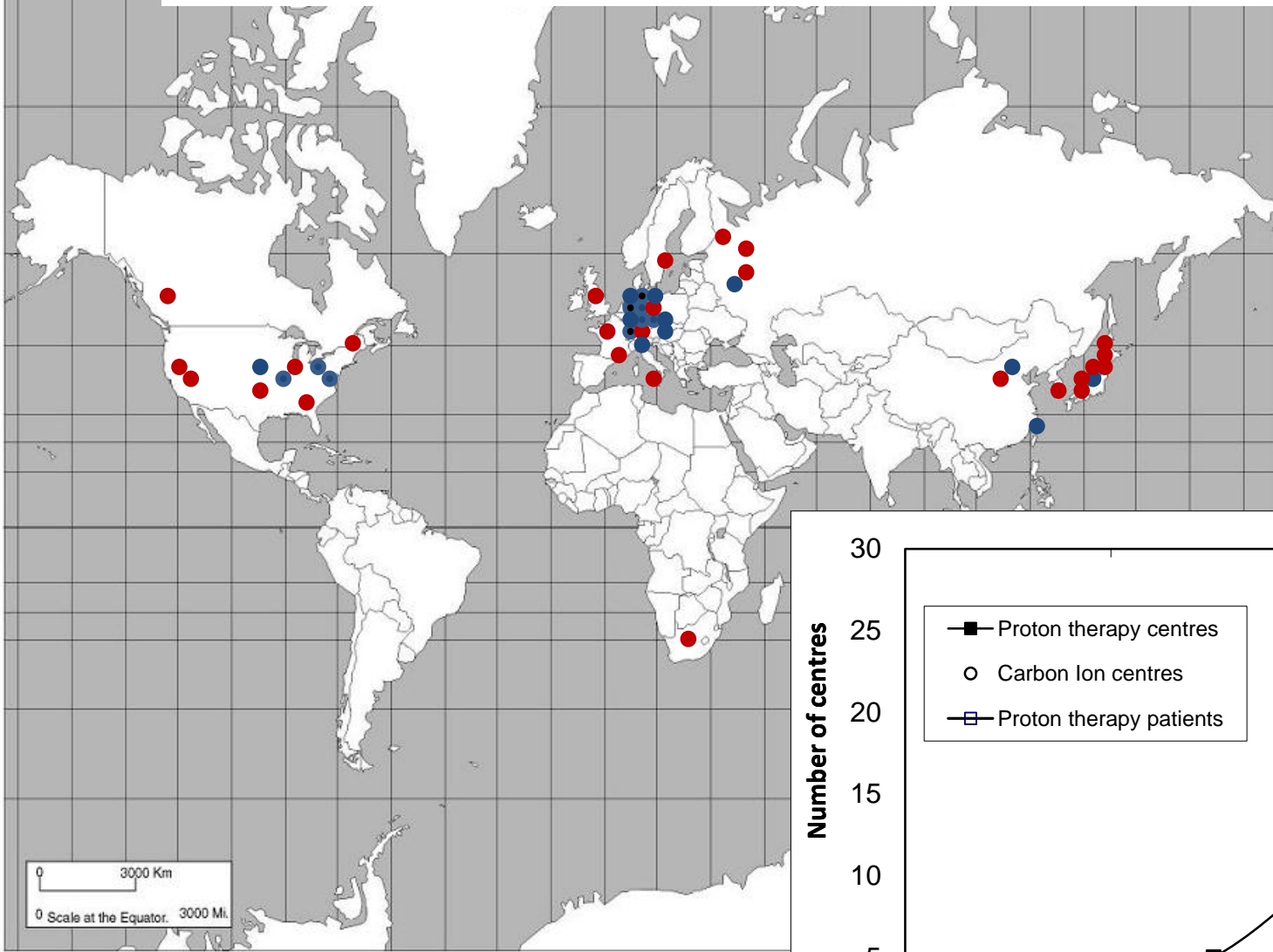


- **First idea**
 - Bob Wilson, 1946 [R. R. Wilson, Radiology 47 (1946) 487]
- **Bragg peak**
 - Better conformity of the dose to the target → healthy tissue sparing
- **Hadrons are charged**
 - Beam scanning for dose distribution
- **Heavy ions**
 - Higher biological effectiveness (RBE)

Part 2: Accelerators and technology

Accelerators for hadrontherapy

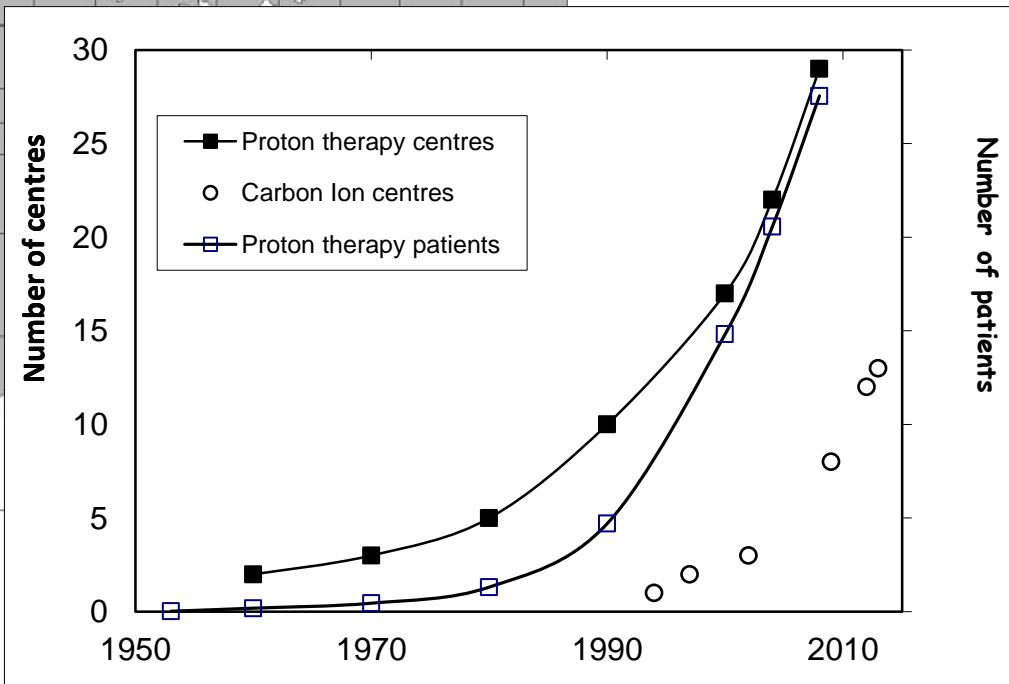
Hadrontherapy centres **IN OPERATION** and **UNDER CONSTRUCTION** worldwide



- Planned/Under construction (25)
 - In operation (42)
- (PTCOG Data)

0 3000 Km
0 Scale at the Equator. 3000 Mi.

M. Dosanjh (PTCOG Data)



The site treated
with hadrons

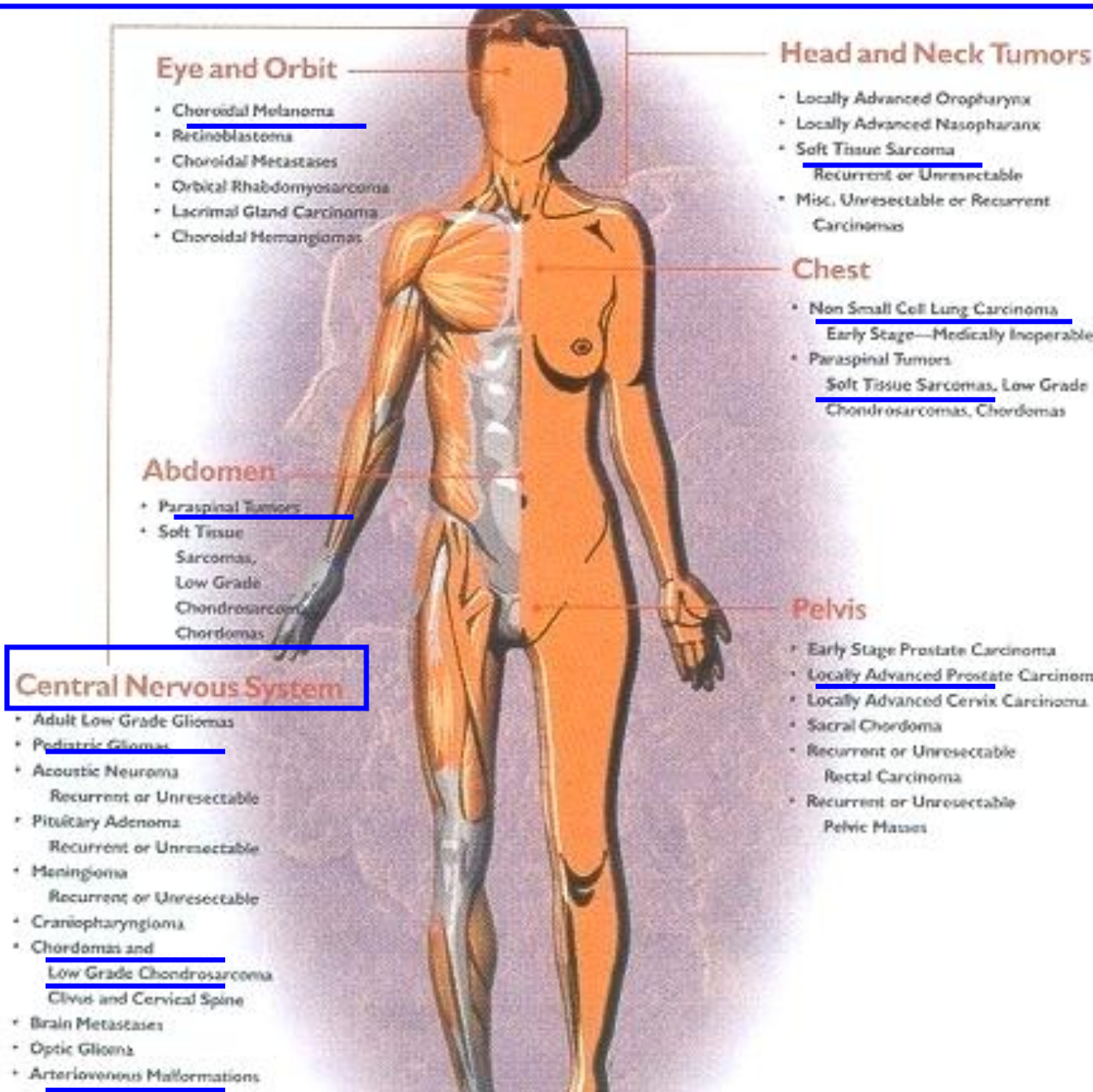
In the world

protons:

- 100'000 patients
- (+10% per year)

carbon ions

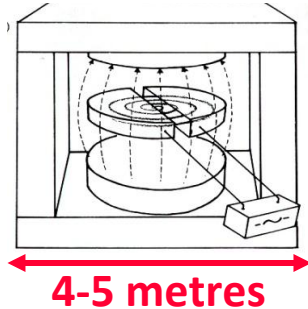
- 8'500 patients



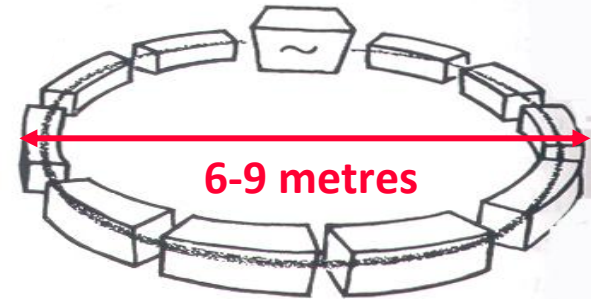
The accelerators used today in hadrotherapy are “circular”

Teletherapy with protons (200-250 MeV)

CYCLOTRONS (*) (Normal or SC)



SYNCHROTRONS



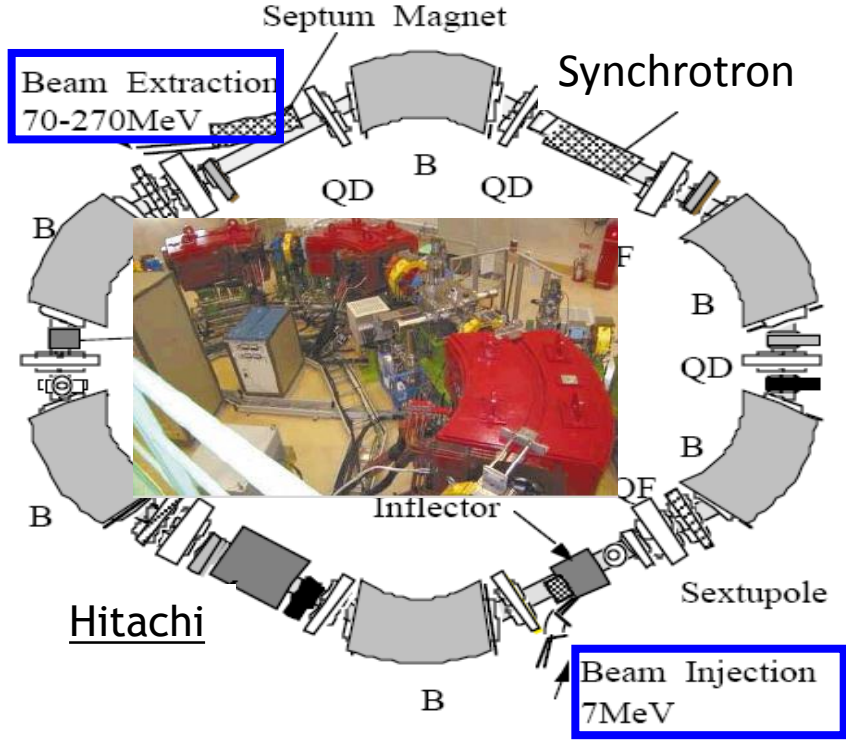
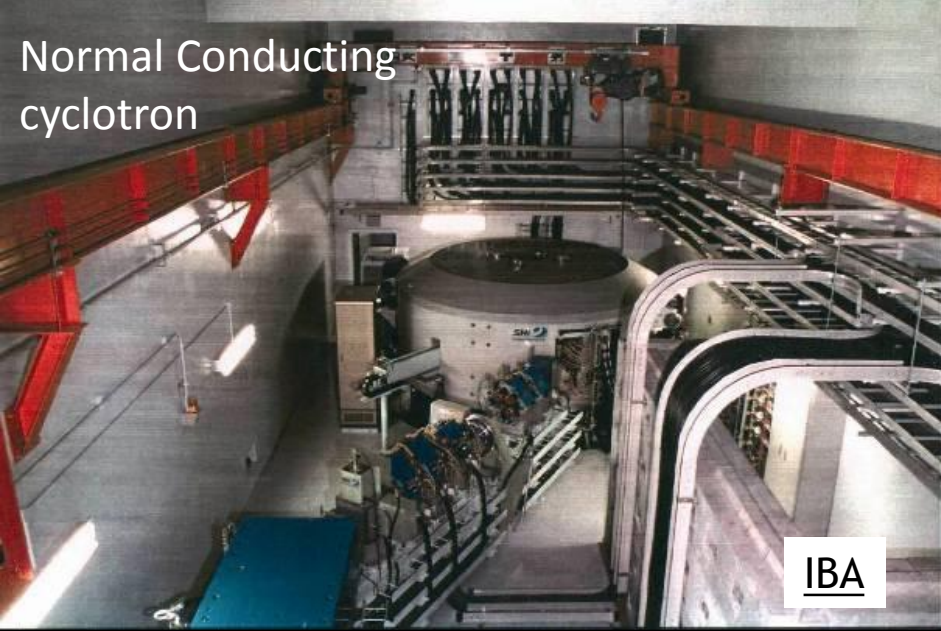
(*) also synchrocyclotrons

Teletherapy with carbon ions (4800 MeV = 400 MeV/u)

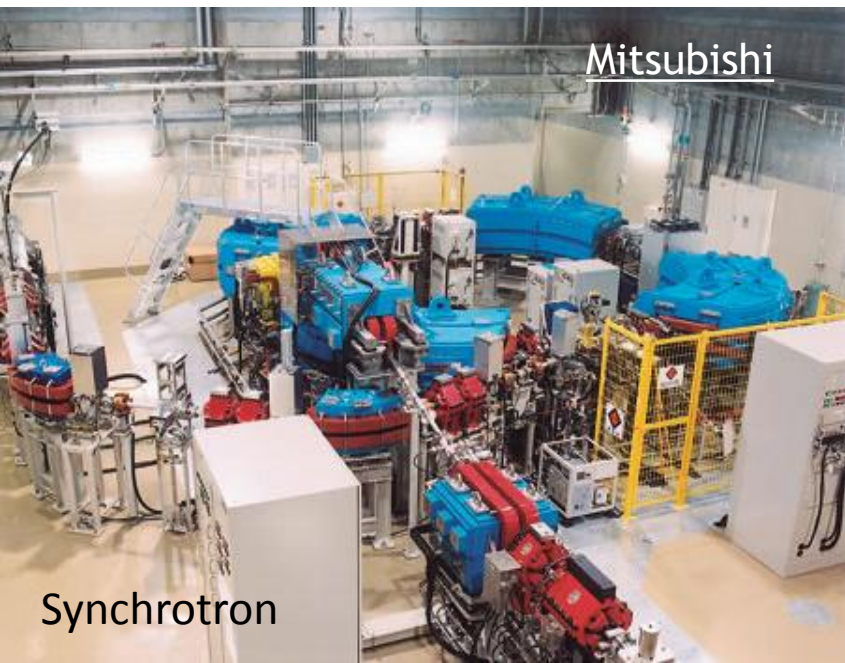
SYNCHROTRONS

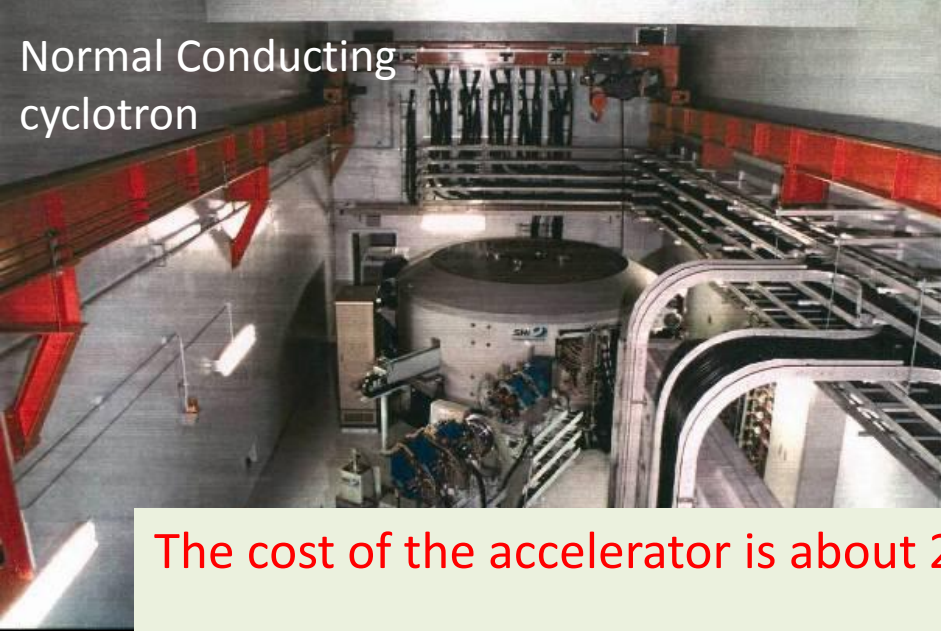


Proton accelerators

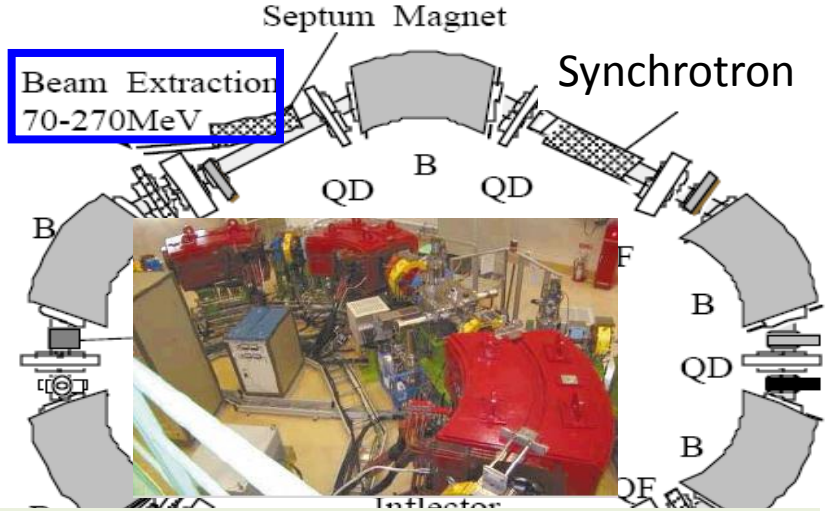


4 commercial 230-250 MeV p⁺ accelerators





Normal Conducting cyclotron



The cost of the accelerator is about 20% of the cost of the centre:

accelerator	20%	
building	20%	
3 gantries	20%	(~30 MEuro)

4 cor

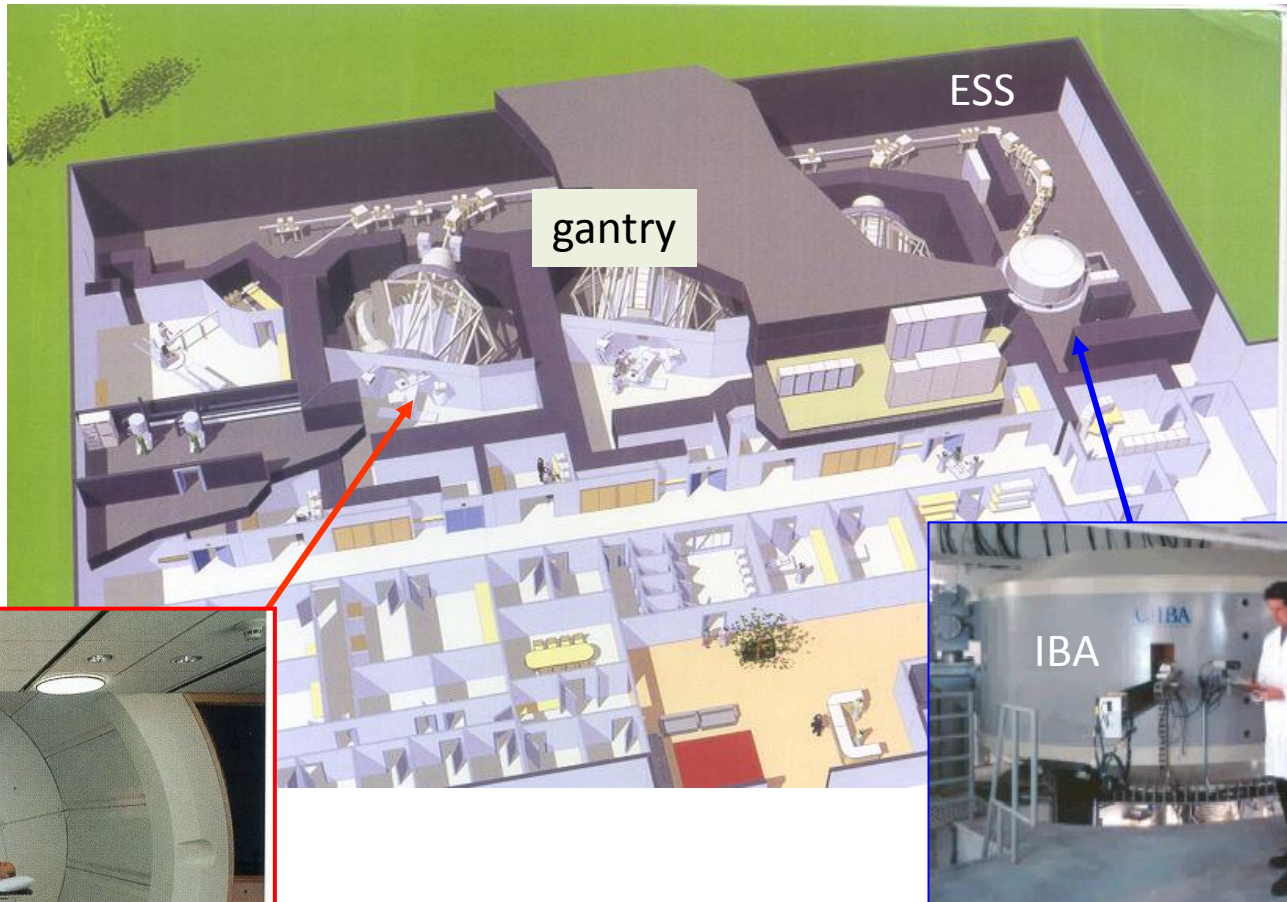


Synchrotron



Varian
SC cyclotron

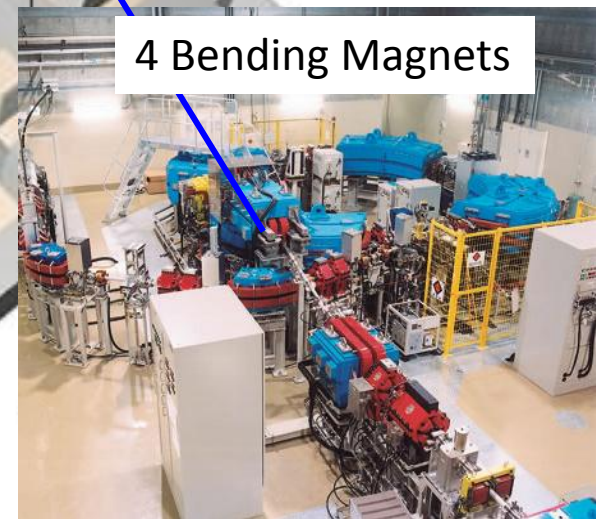
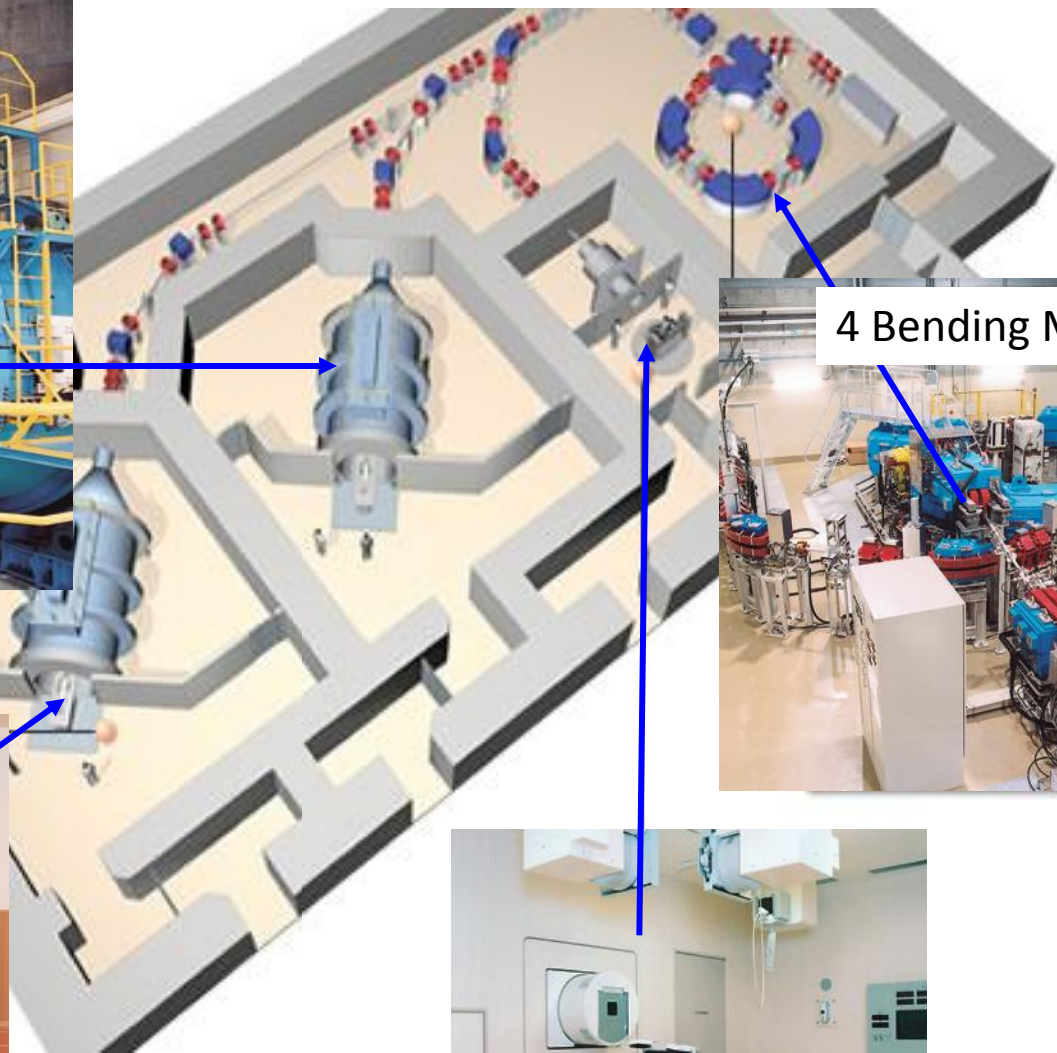
Cyclotron for protons by Ion Beam Applications - Belgium



Turn-key centres are offered for $\approx 150-180$ M€.

If proton accelerators were 'small' and 'cheap',
no radiation oncologist would use X rays.

Mitsubishi solution for Shizuoka - Japan



Rinecker Proton Therapy Centre Munich



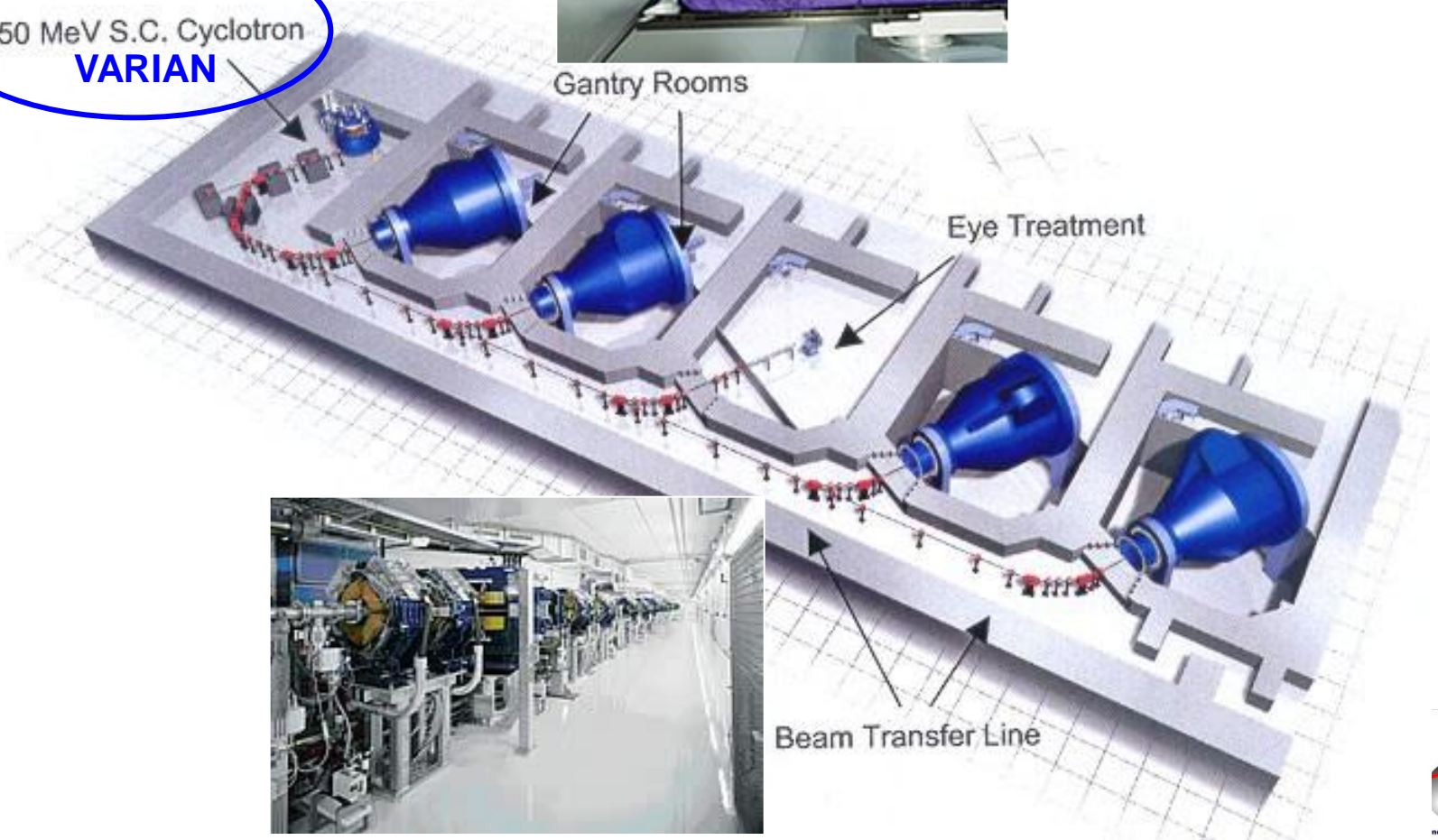
250 MeV S.C. Cyclotron
VARIAN



Gantry Rooms

Eye Treatment

Beam Transfer Line



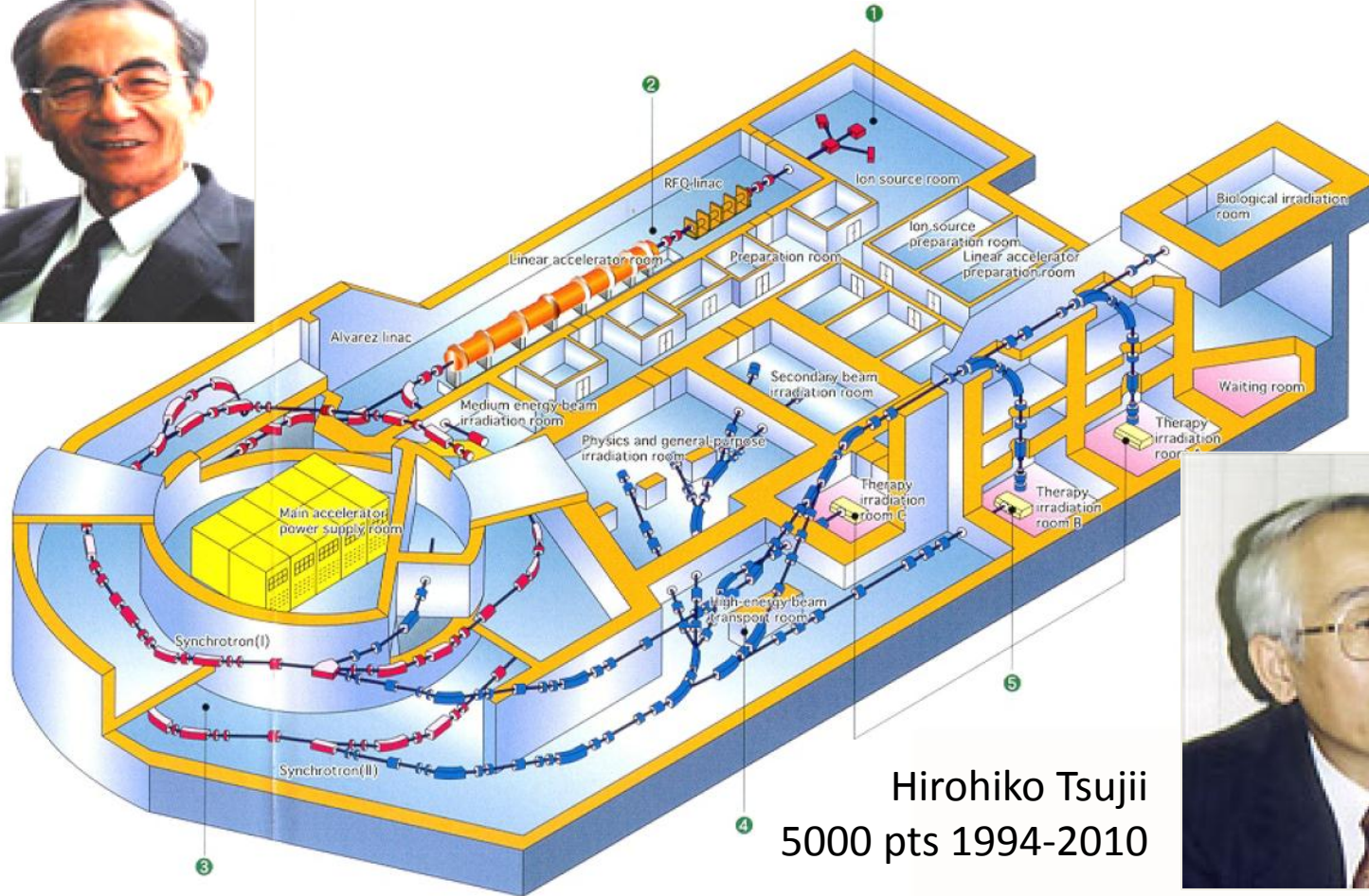
**Dual centers
(p^+ / C^{6+} accelerators)**

HIMAC in Chiba is the pioneer of carbon therapy

Yasuo Hirao



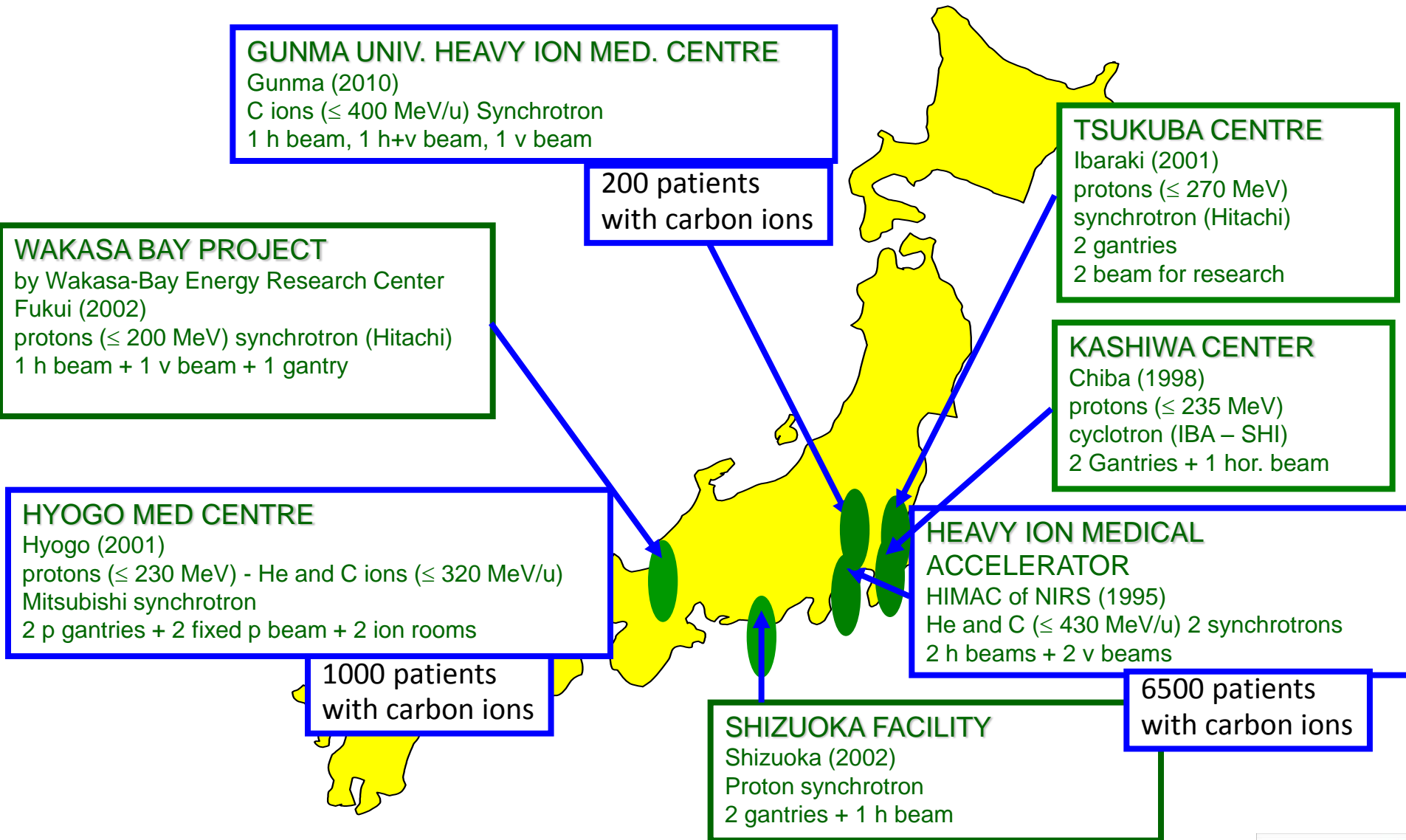
¹⁵ Hirao, Y. et al, "Heavy Ion Synchrotron for Medical Use: HIMAC Project at NIRS Japan" Nucl. Phys. A538, 541c (1992)



Hirohiko Tsujii
5000 pts 1994-2010

Since the cells do not repair. less fractions are possible
HIMAC: 4-9 fractions!

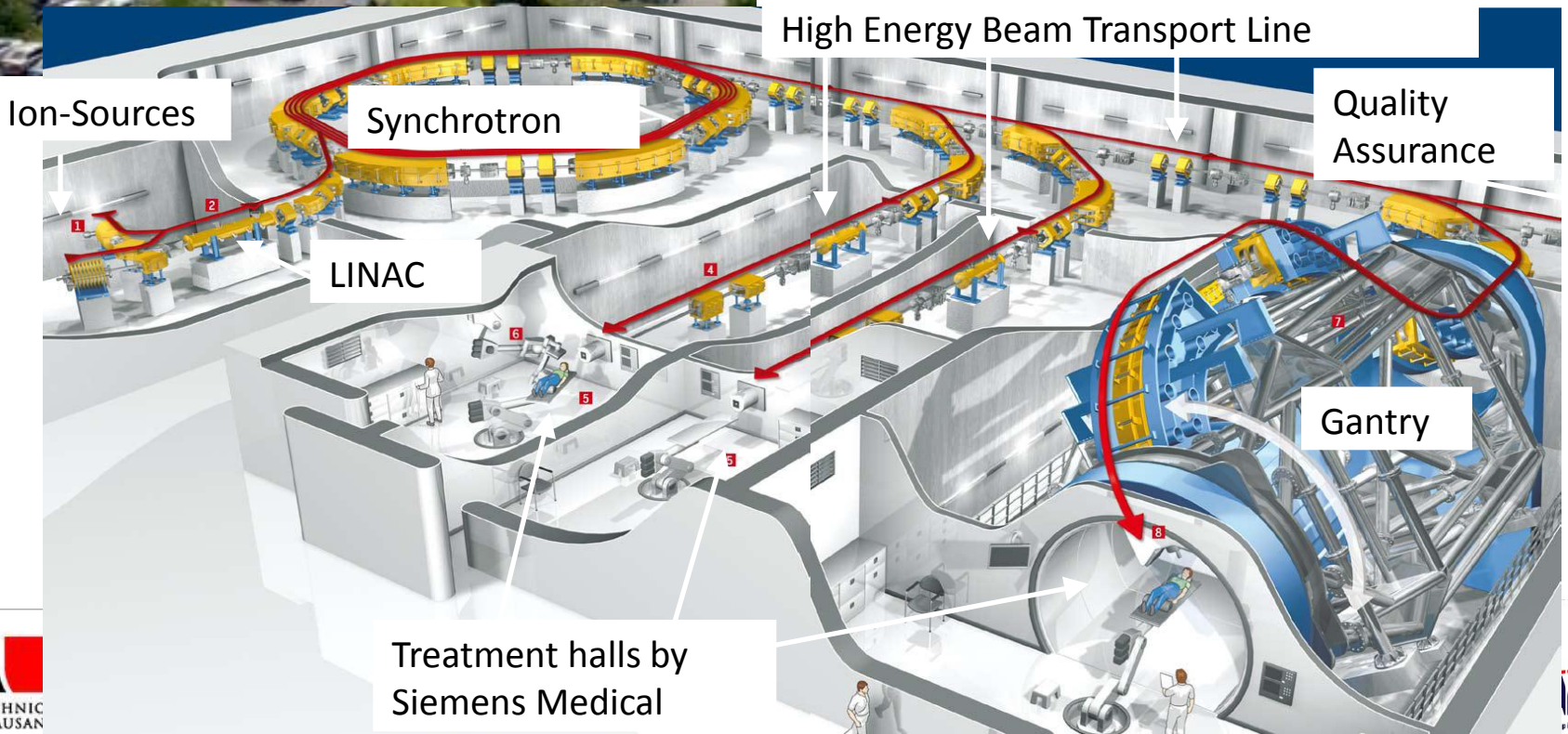
Japan is the best equipped region



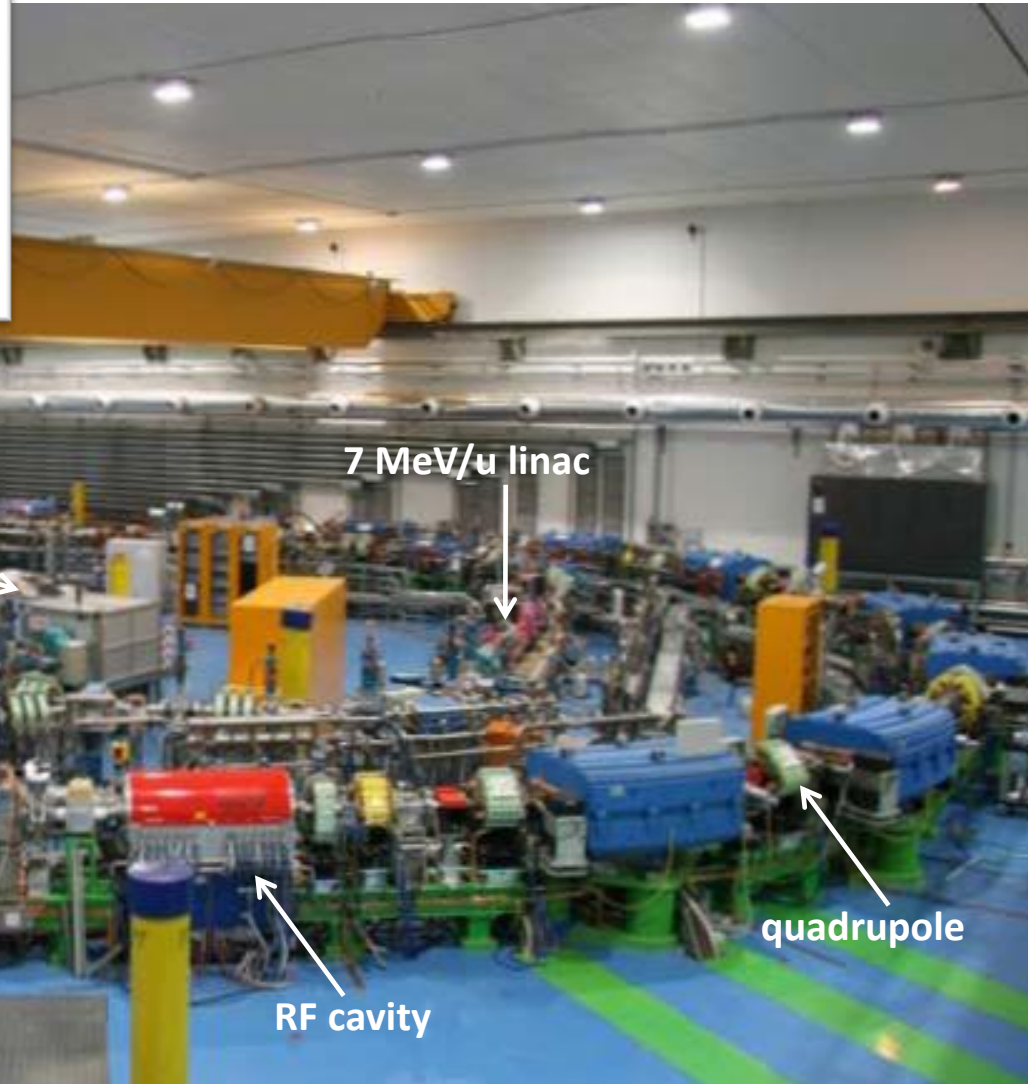
HIT at Heidelberg

Medical Director: J. Debus
Technical Director: T. Haberer

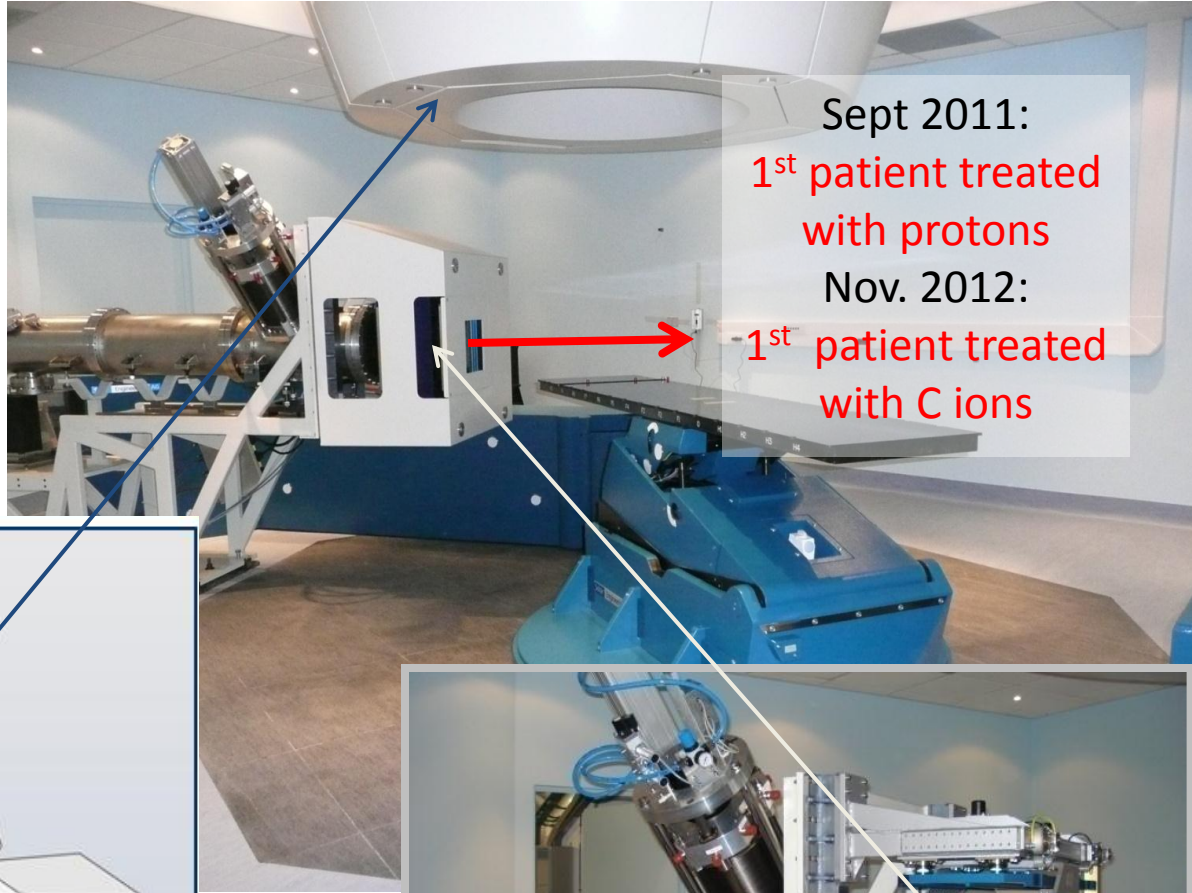
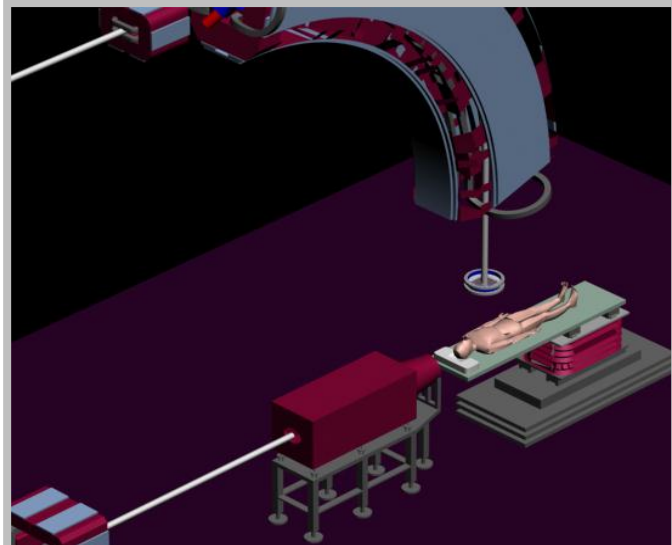
First patient: September 2009
At present: about 600 patients



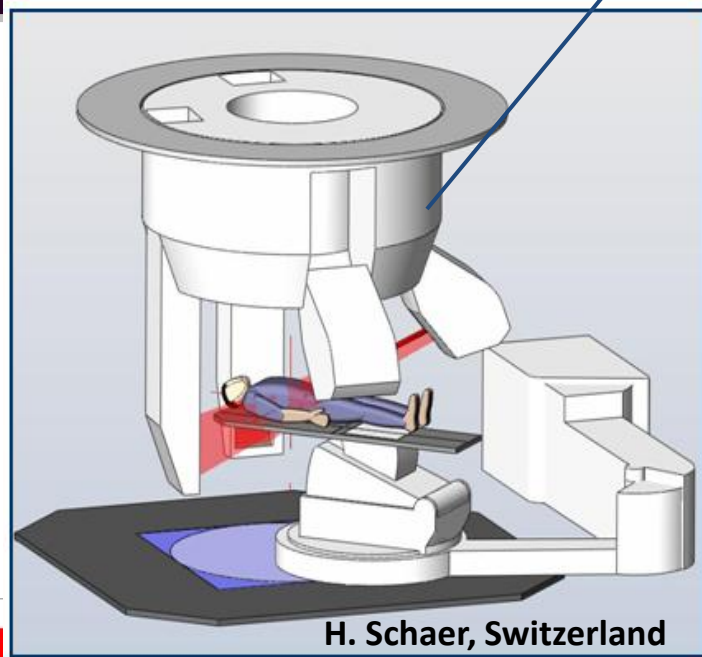
CNAO: Centro Nazionale Adroterapia Oncologica at Pavia



CNAO: the treatment room



Sept 2011:
1st patient treated
with protons
Nov. 2012:
1st patient treated
with C ions



H. Schaer, Switzerland

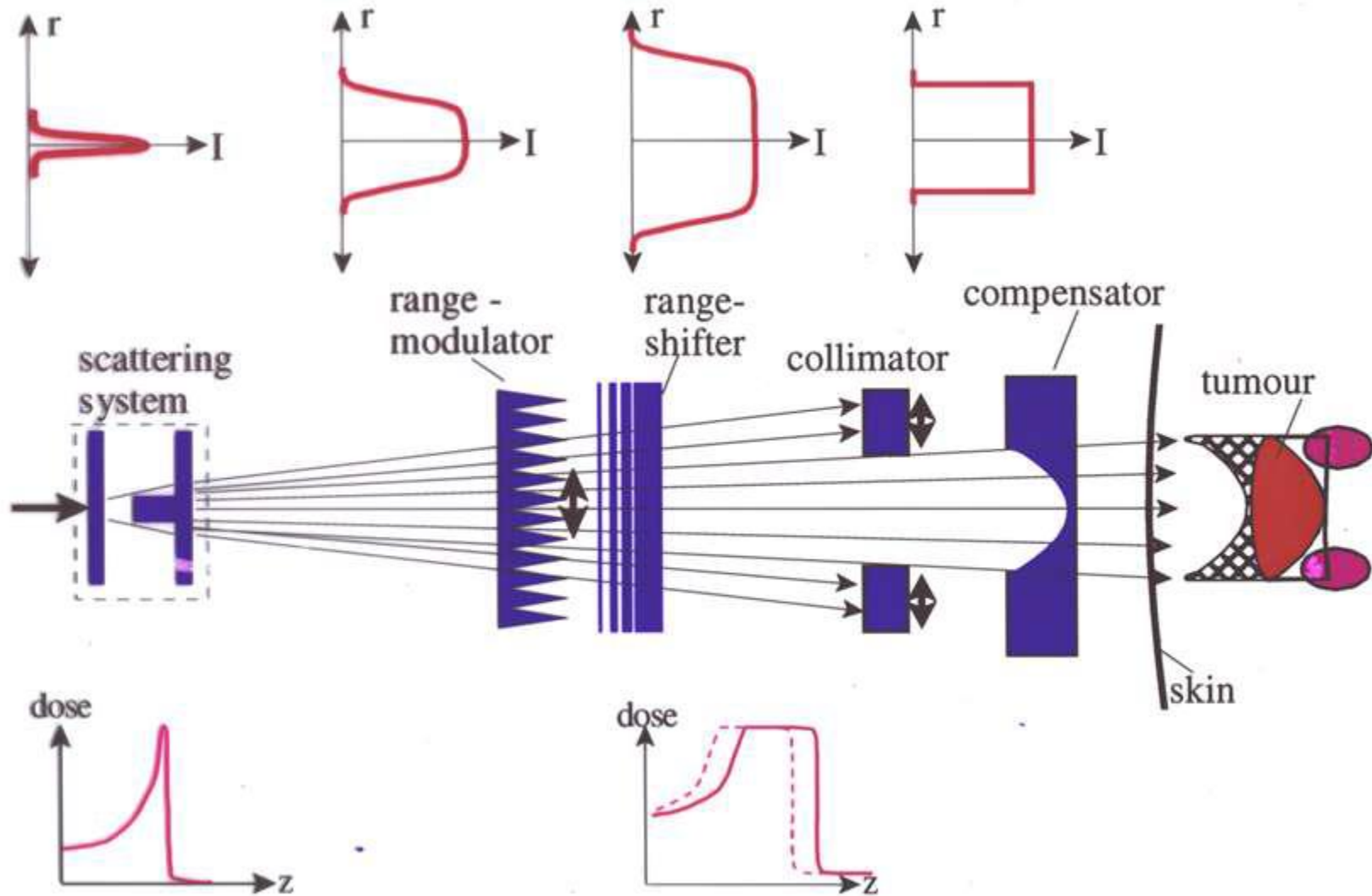


Part 2: Accelerators and technology

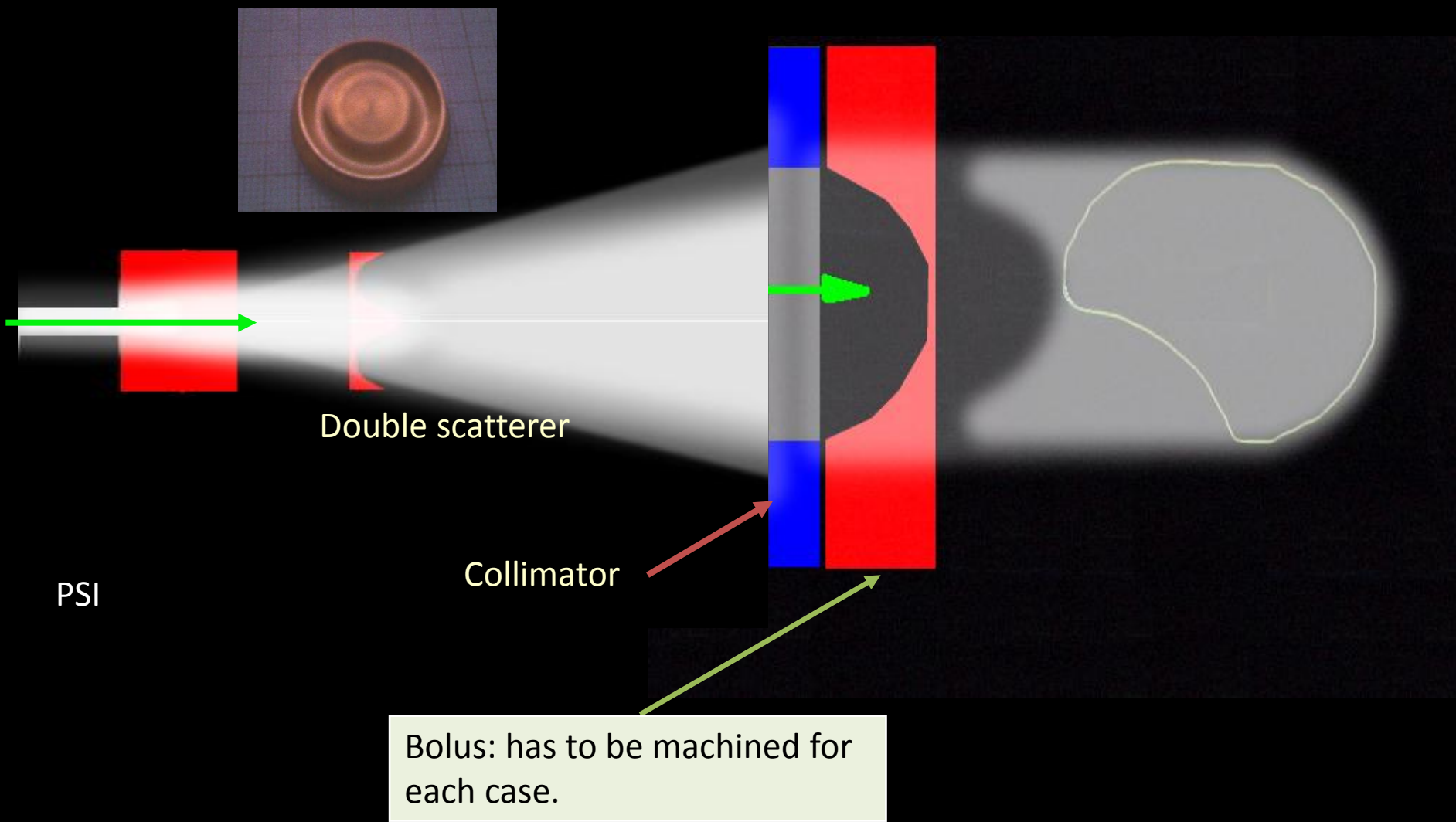
Treatment modalities

Two methods for imparting the dose:

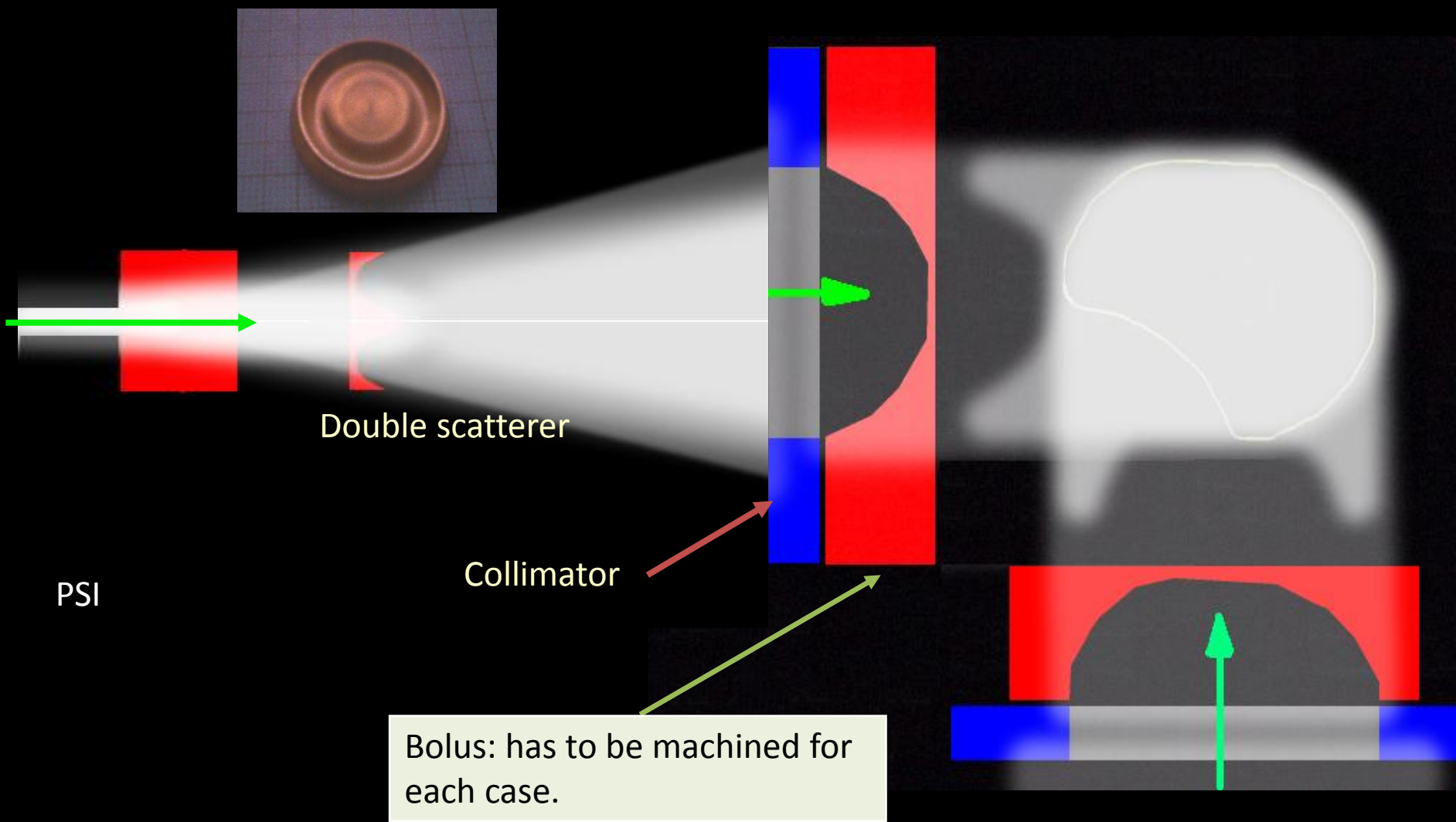
1A. Passive beam spreading



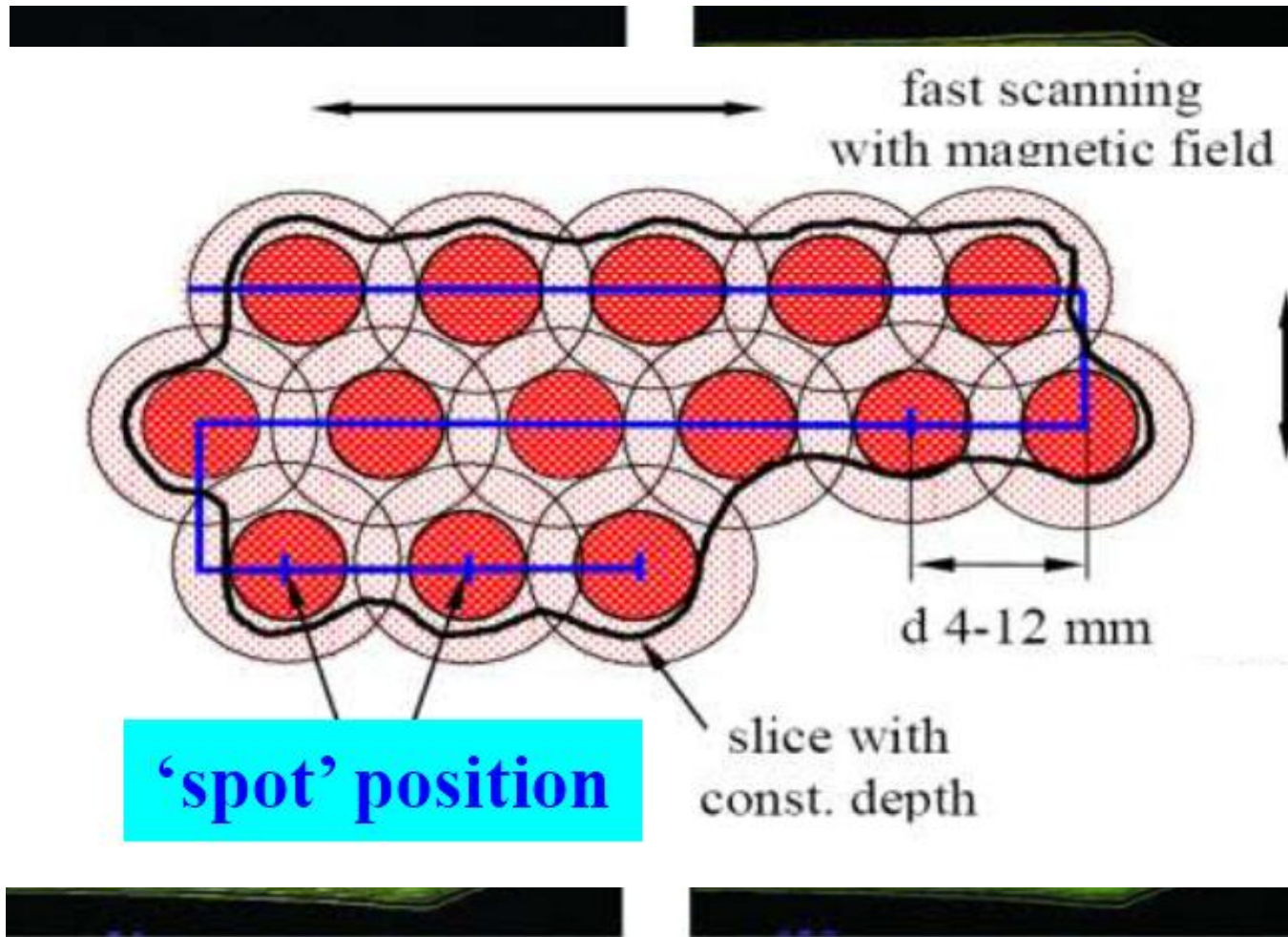
1A. Standard procedure: Passive beam spreading with respiratory gating



1A. Standard procedure: Passive beam spreading with respiratory gating



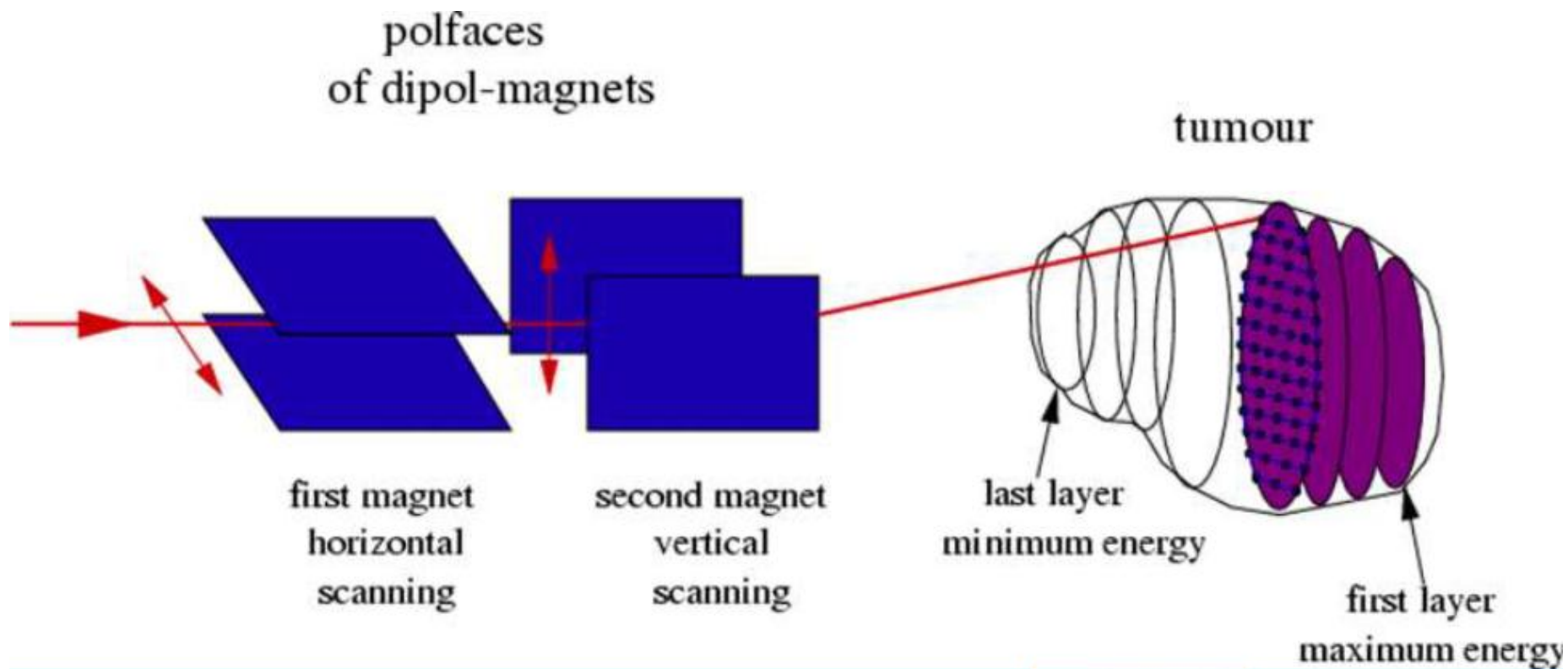
2A. Active “spot scanning” technique by PSI with respiratory gating (Villigen)



Depth scanning: ENERGY
MODULATION

3D conformal treatment

2B. Active “raster scanning” technique by GSI with respiratory gating (Villigen)



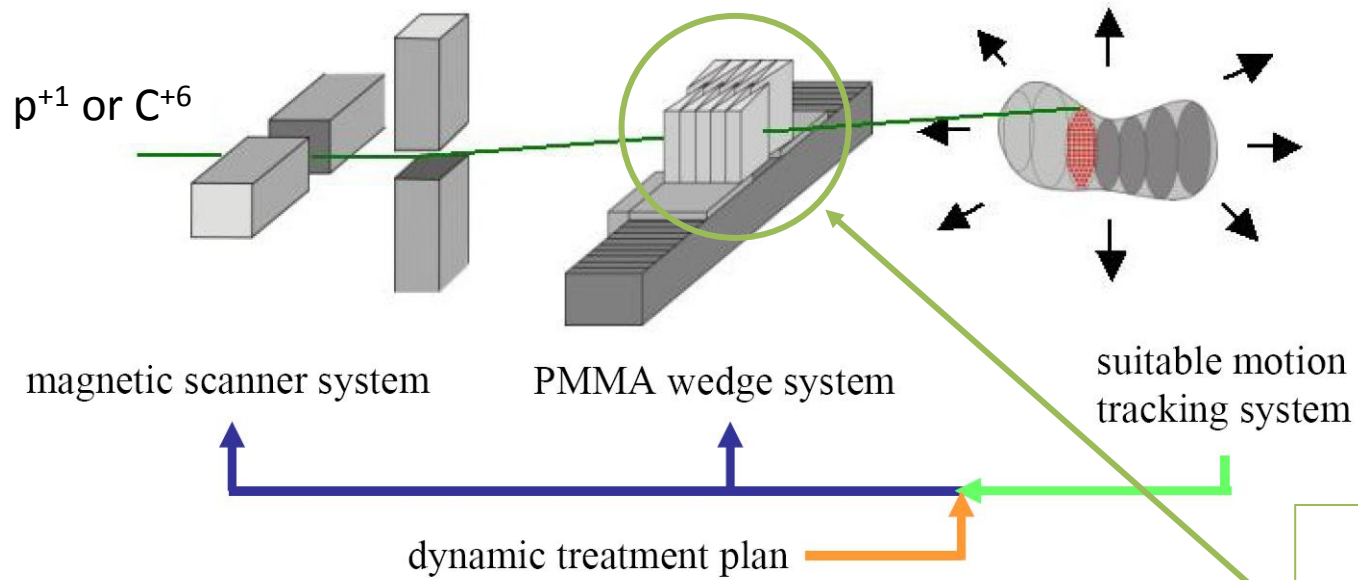
The synchrotron beam is moved continuously

Part 2: Accelerators and technology

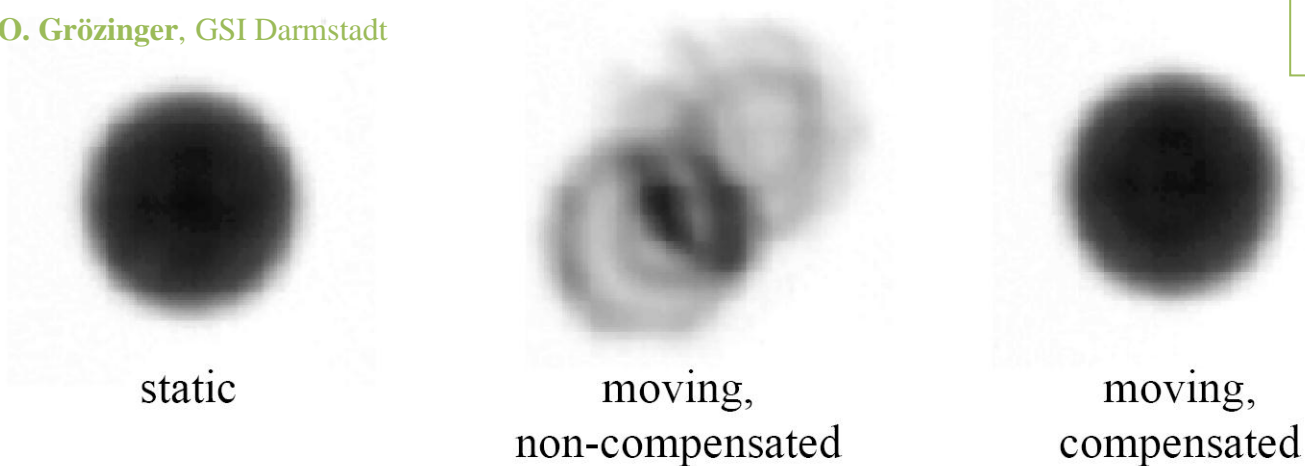
Future challenges in hadrontherapy

1. Treating moving organs

GSI approach depth scanning with fast absorbers



Sven O. Grözinger, GSI Darmstadt



2nd challenge: proton single room-facilities

The reasons for proton single room-facilities*:

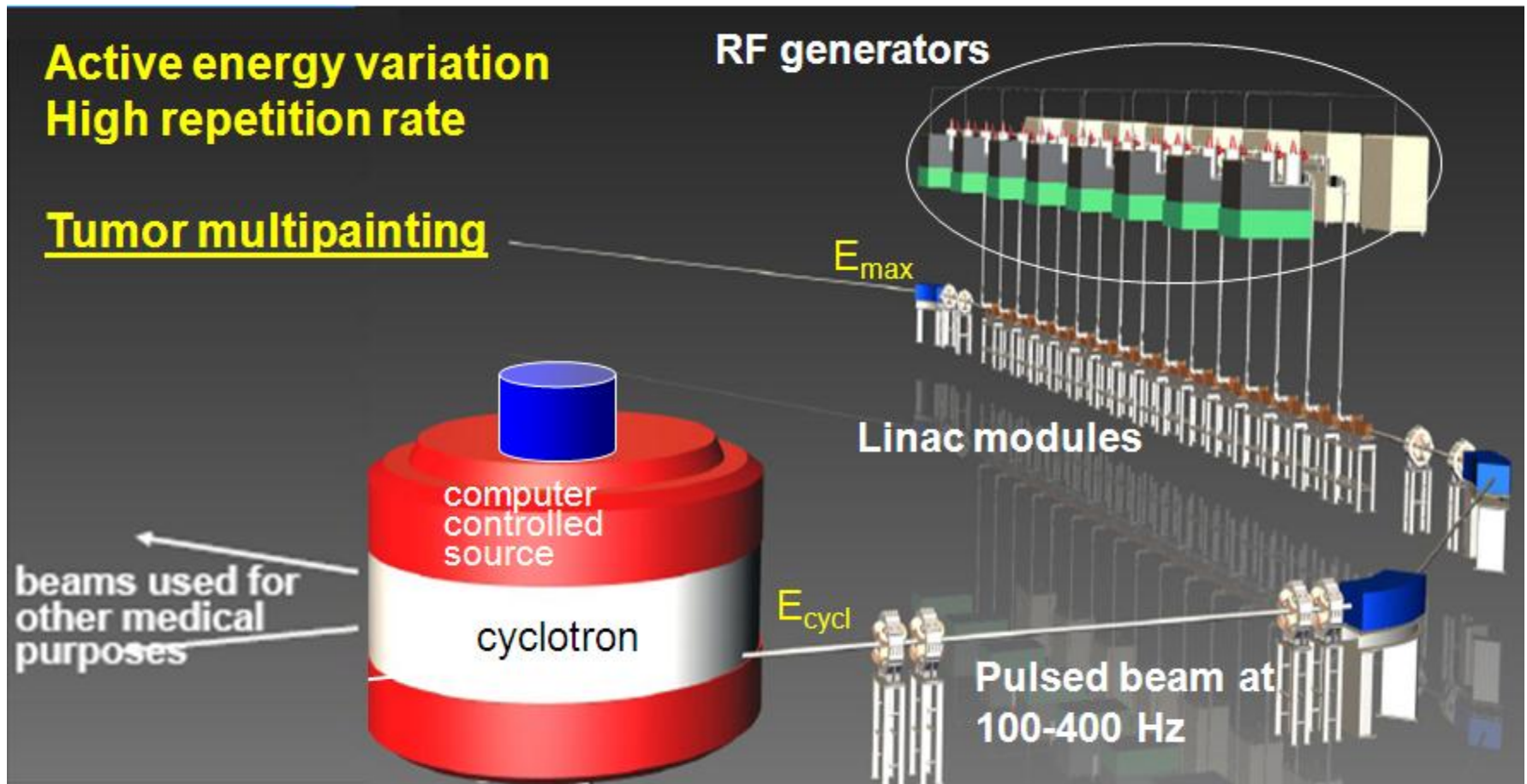
Radiation treatment	Patients per year in 10 ⁷	Number of session per patient	Sessions/d in 1 room (d = 12 h)	Patients/y in 1 room (y=230 d)	Rooms per 10 million people ⁽¹⁾	Relative ratio ~
Photons ⁽¹⁾	20'000	30	48	370	54	8 ²
Protons (12%)	2'400	20	36	380	6.3	8
C ions (3%)	600	10	36	760	0.8	1

ENLIGHT results

1 Proton single-room facility every 8 X-ray rooms in 3-4 close-by hospitals serving ≤2 million people

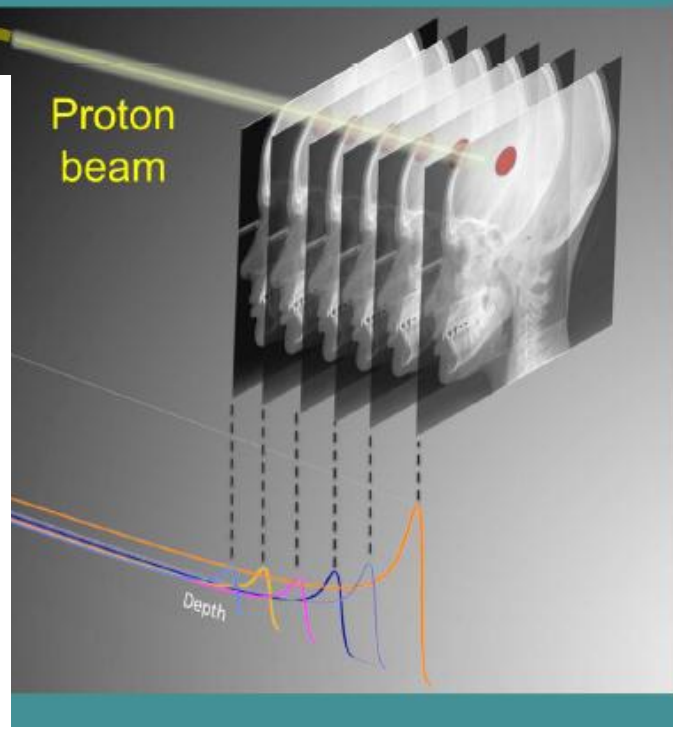
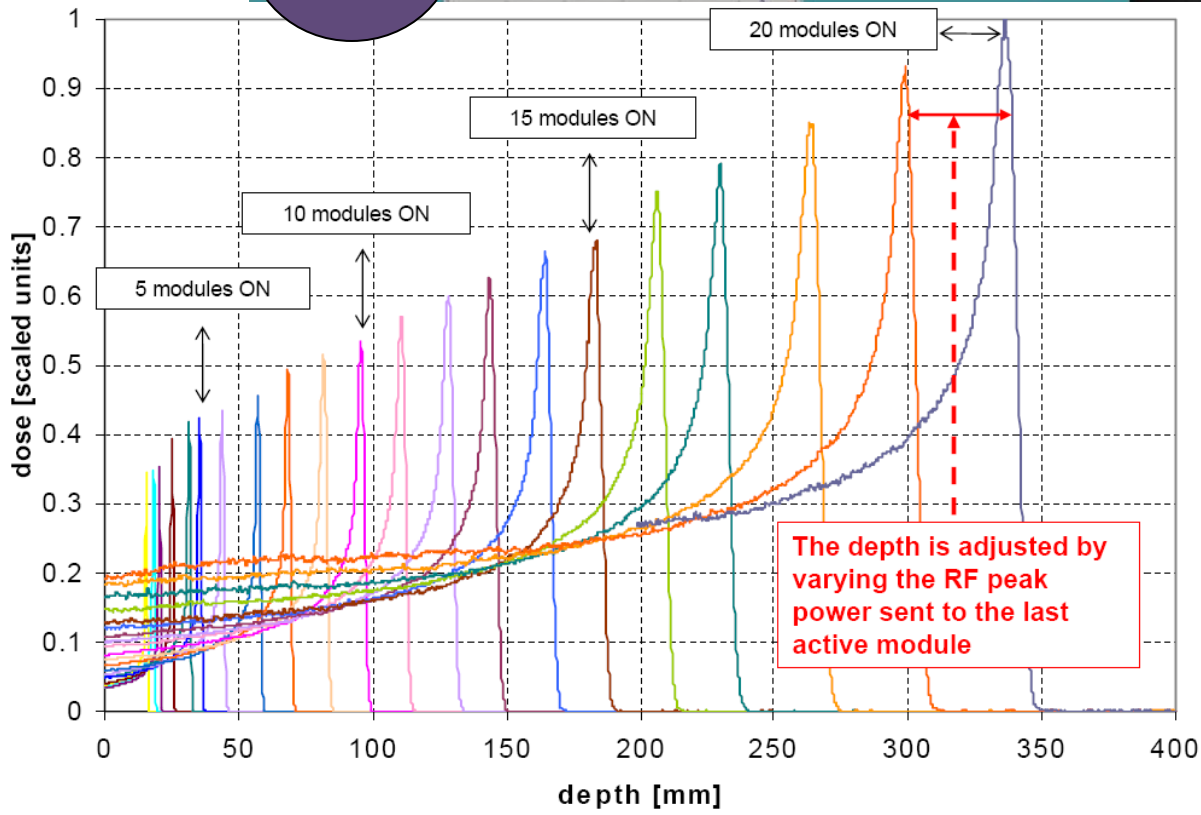
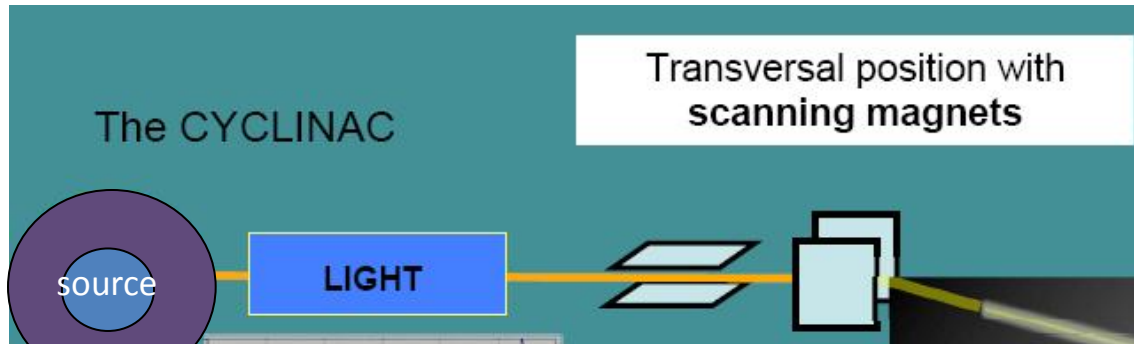
* U. Amaldi et. al, NIM A 620 (2010), 563-577

TERA approach to treat moving organs and for single room facilities: the CYCLINAC



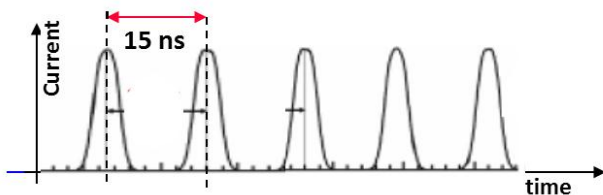
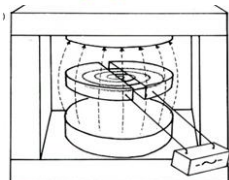
Beam suitable for the 4D spot scanning technique

The energy of a cyclinac can be varied in 1-2 ms



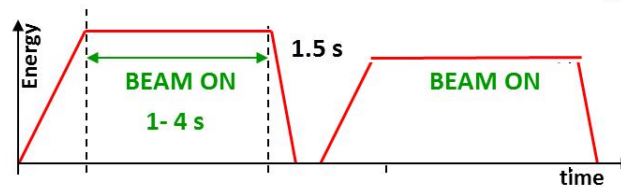
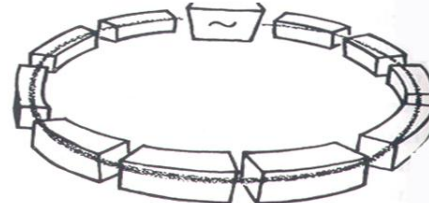
Properties of the beams of different accelerators

CYCLOTRONS (*) (Normal or SC)



The pulsed beam of **fixed energy** is always present

SYNCHROTRONS



A cycling beam of **variable energy** has 1 second gaps

Accelerator type	Beam always present ?	Energy variation by electronic means	Time needed for varying the energy
Cyclotron	Yes (MHz)	No	80-100 ms (with abs)
Synchrotron	No	Yes	1-2 second

Properties of the beams of different accelerators

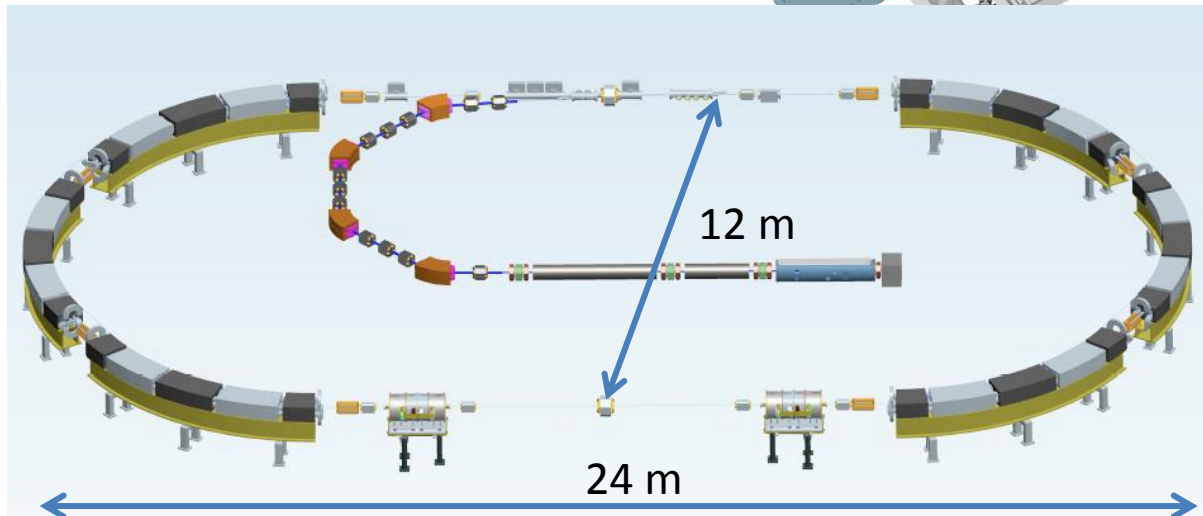
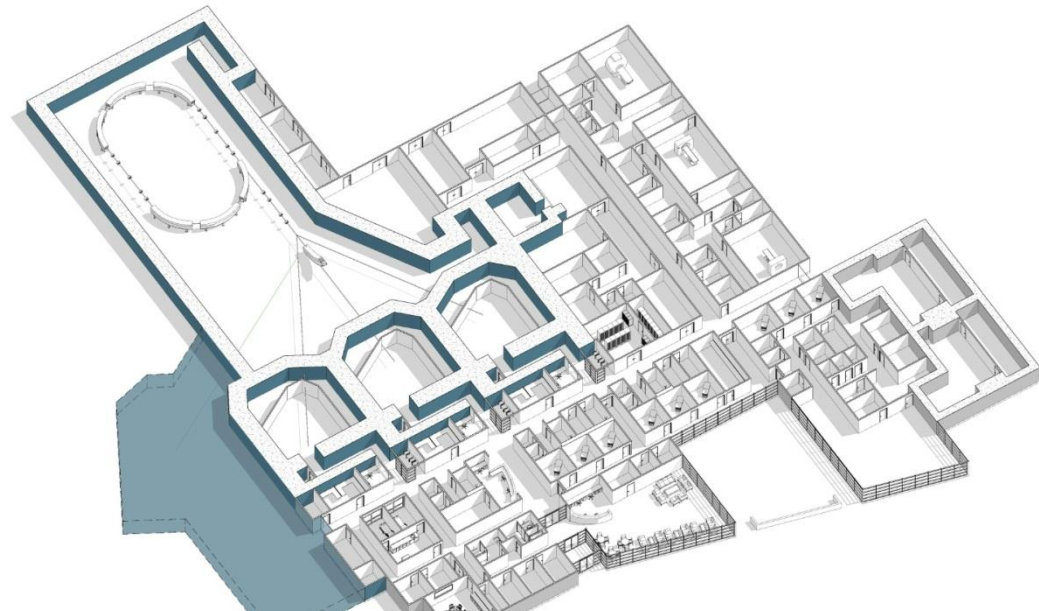
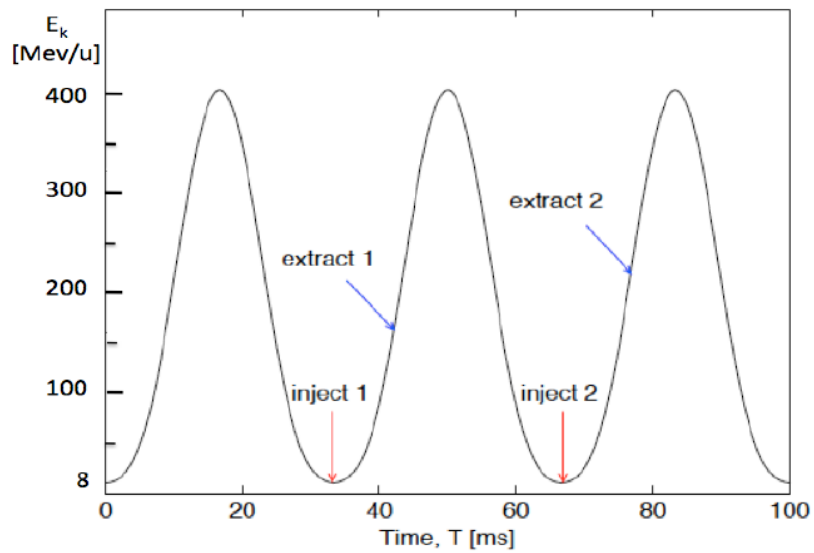
Accelerator type	Beam always present during treatment ?	Energy variation by electronic means	Time needed for varying the energy
Cyclotron	Yes	No	80-100 ms (*)
Synchrotron	No	Yes	1-2 second
Cyclinac	Yes	Yes	1-2 ms

The energy is varied by adjusting the RF pulses to the modules and allows 10 paintings

(*) With advanced movable absorbers

Novel accelerators and gantries designs

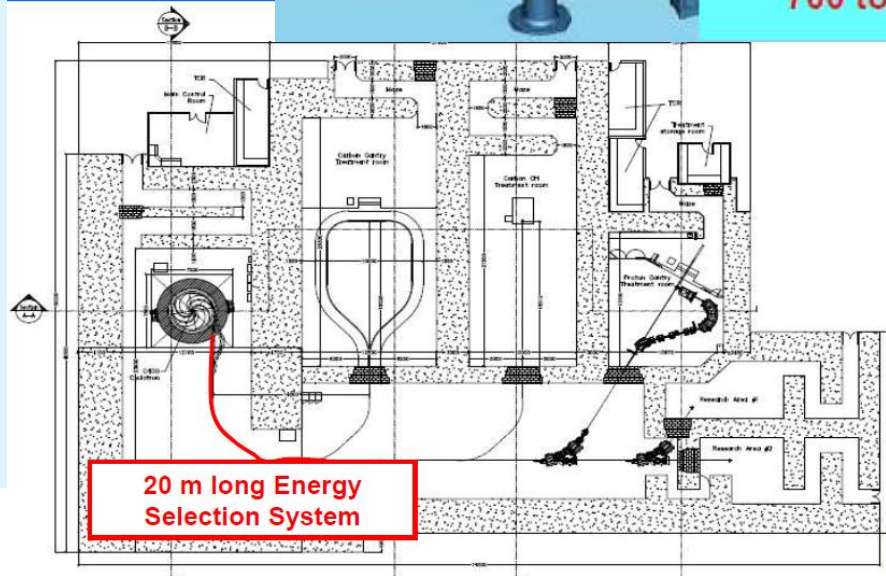
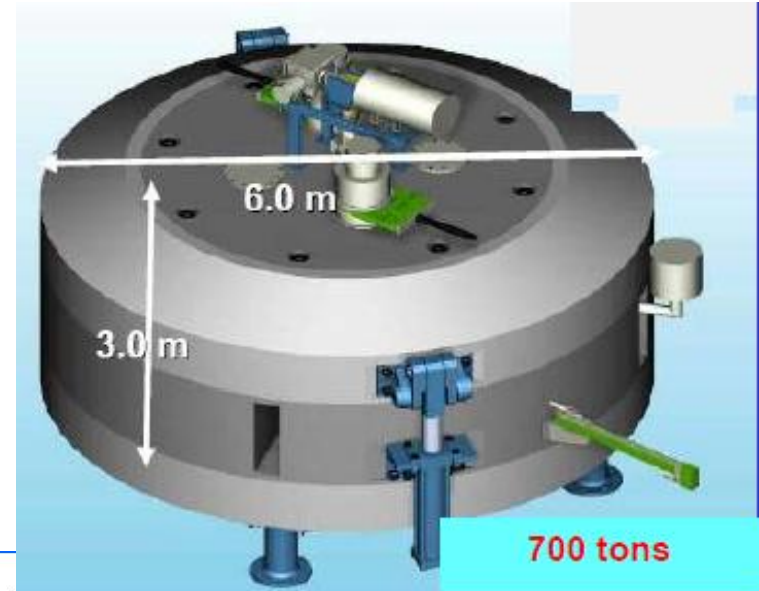
Dual Best Particle Therapy centre (BNL)



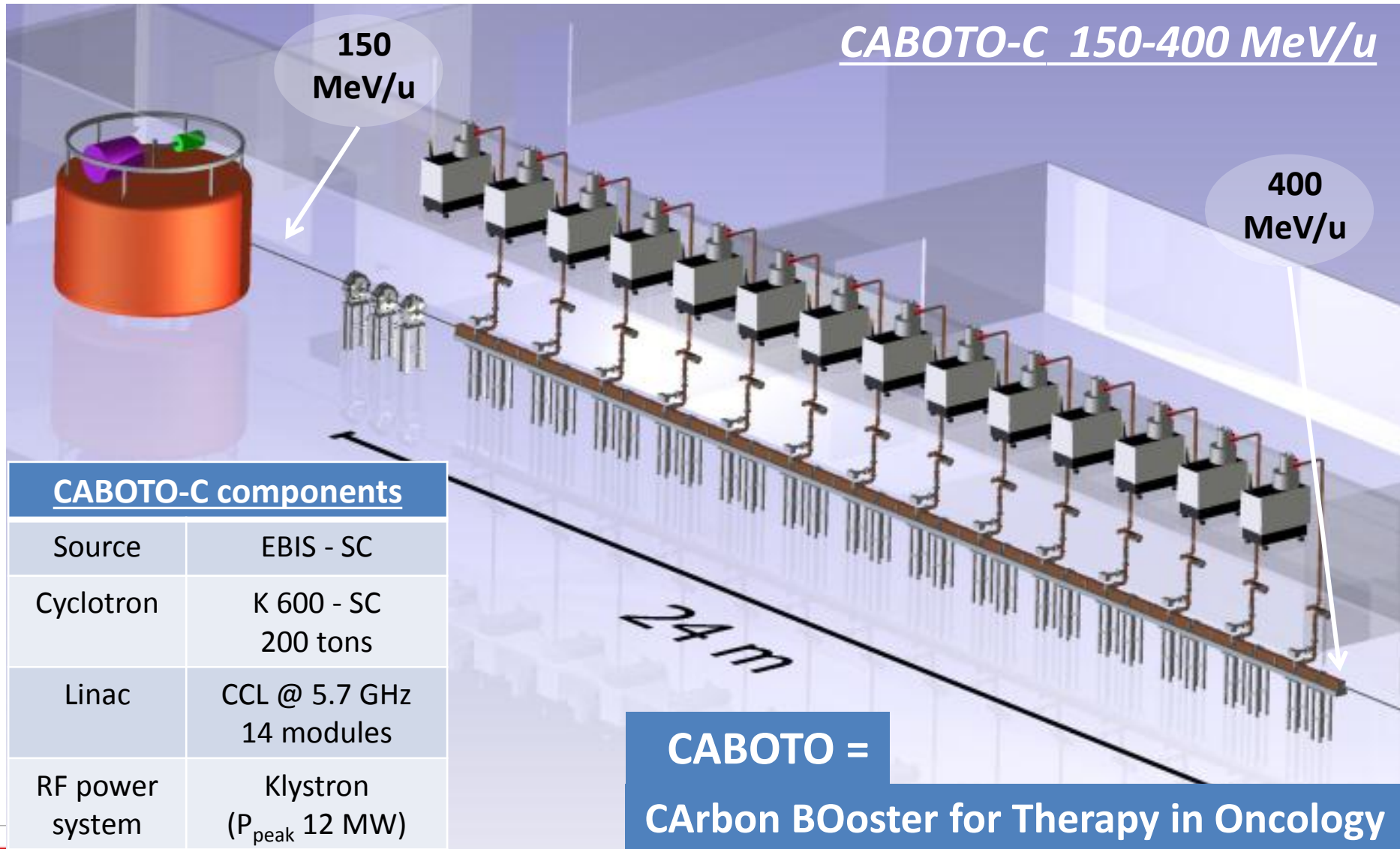
IBA Superconducting cyclotron for carbon, helium and protons



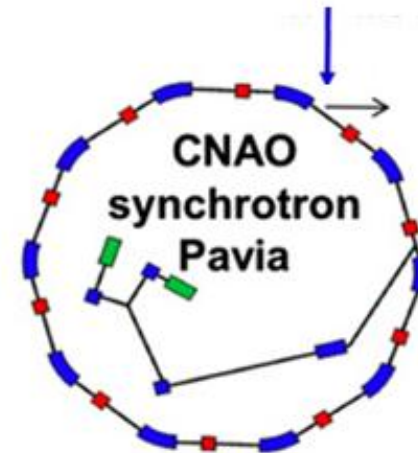
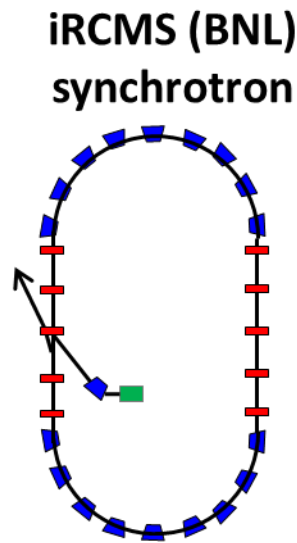
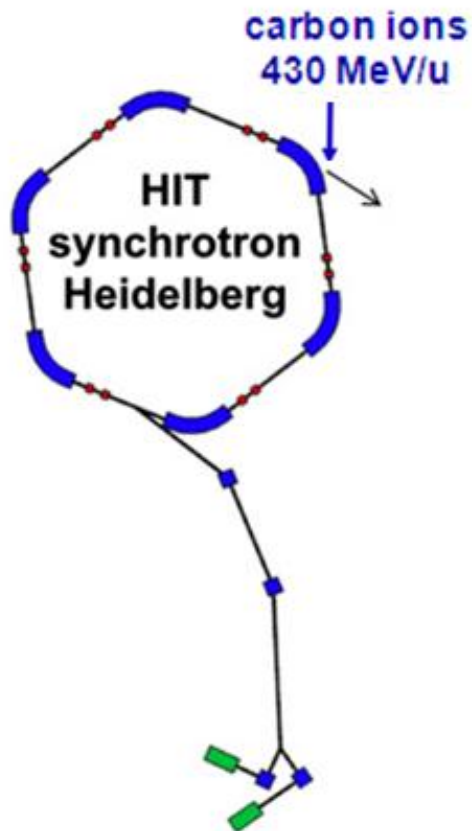
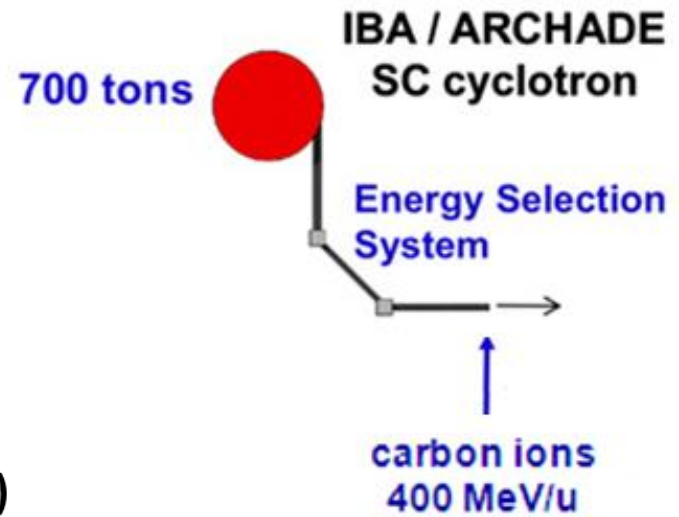
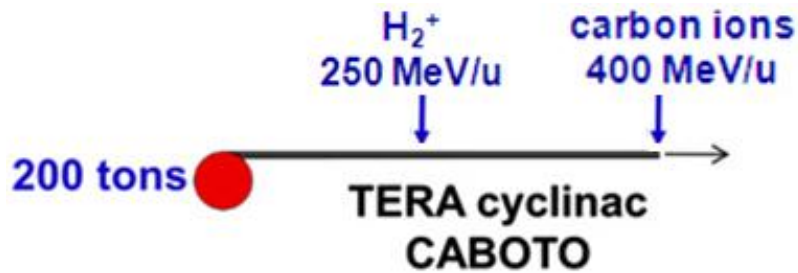
IBA C400 Cyclotron :
400MeV/u carbon , 265 MeV p
($B_c = 4.5$ T)



CABOTO-C: a cyclinac for a compact 'dual' machine



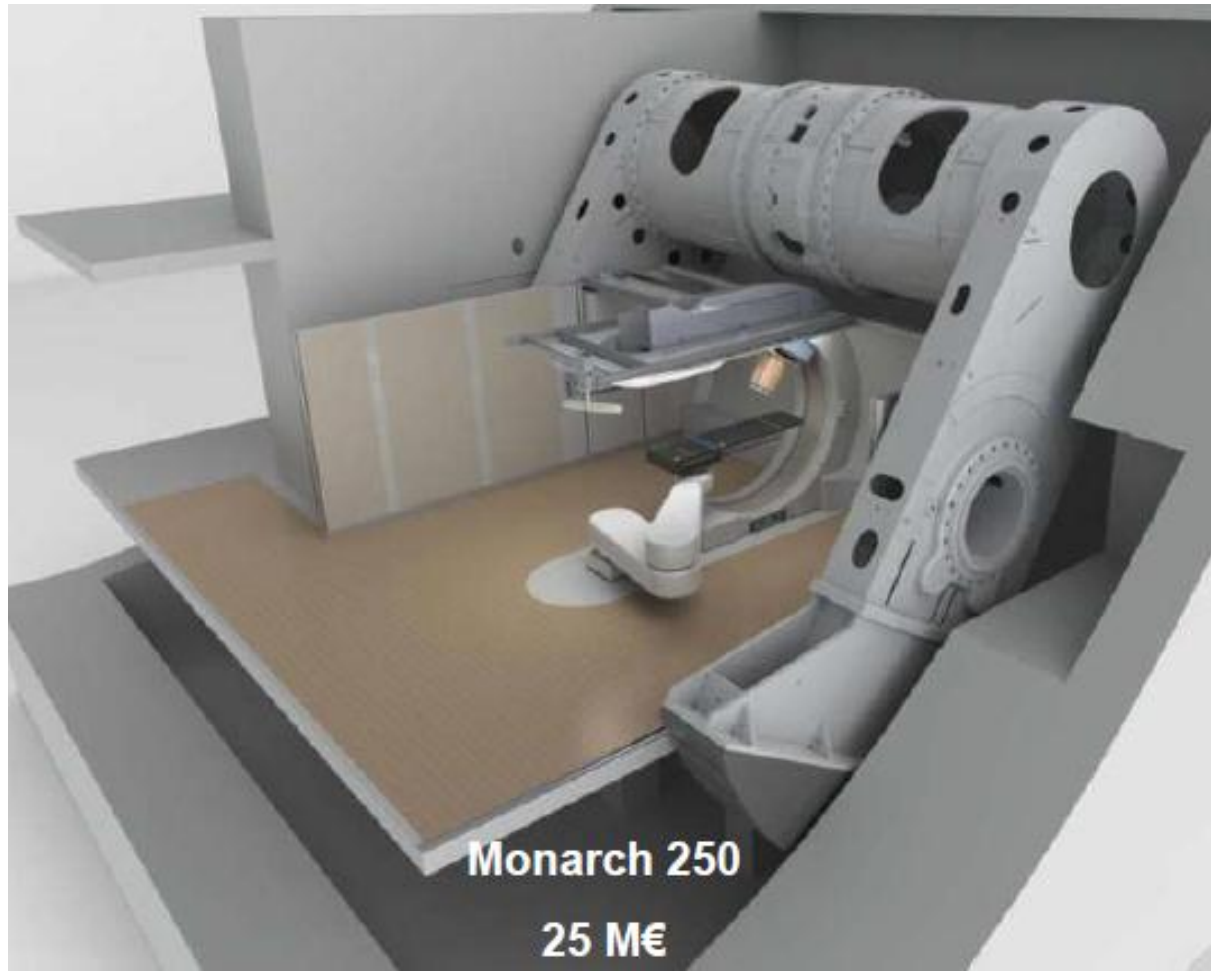
Dimensional comparison among carbon ion accelerators



Proton single room facility by Mevion



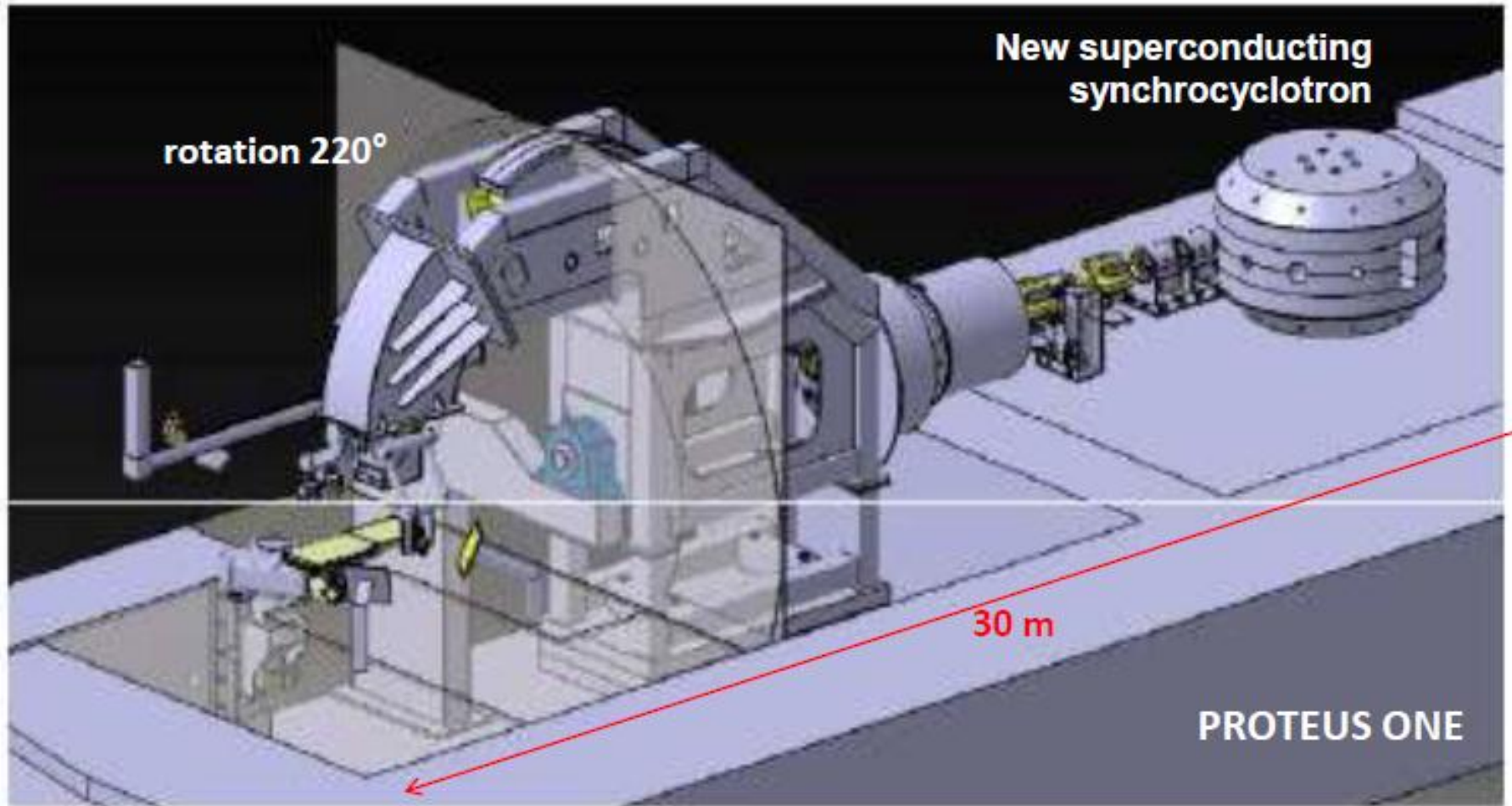
**9 T superconducting
Synchro-cyclotron**



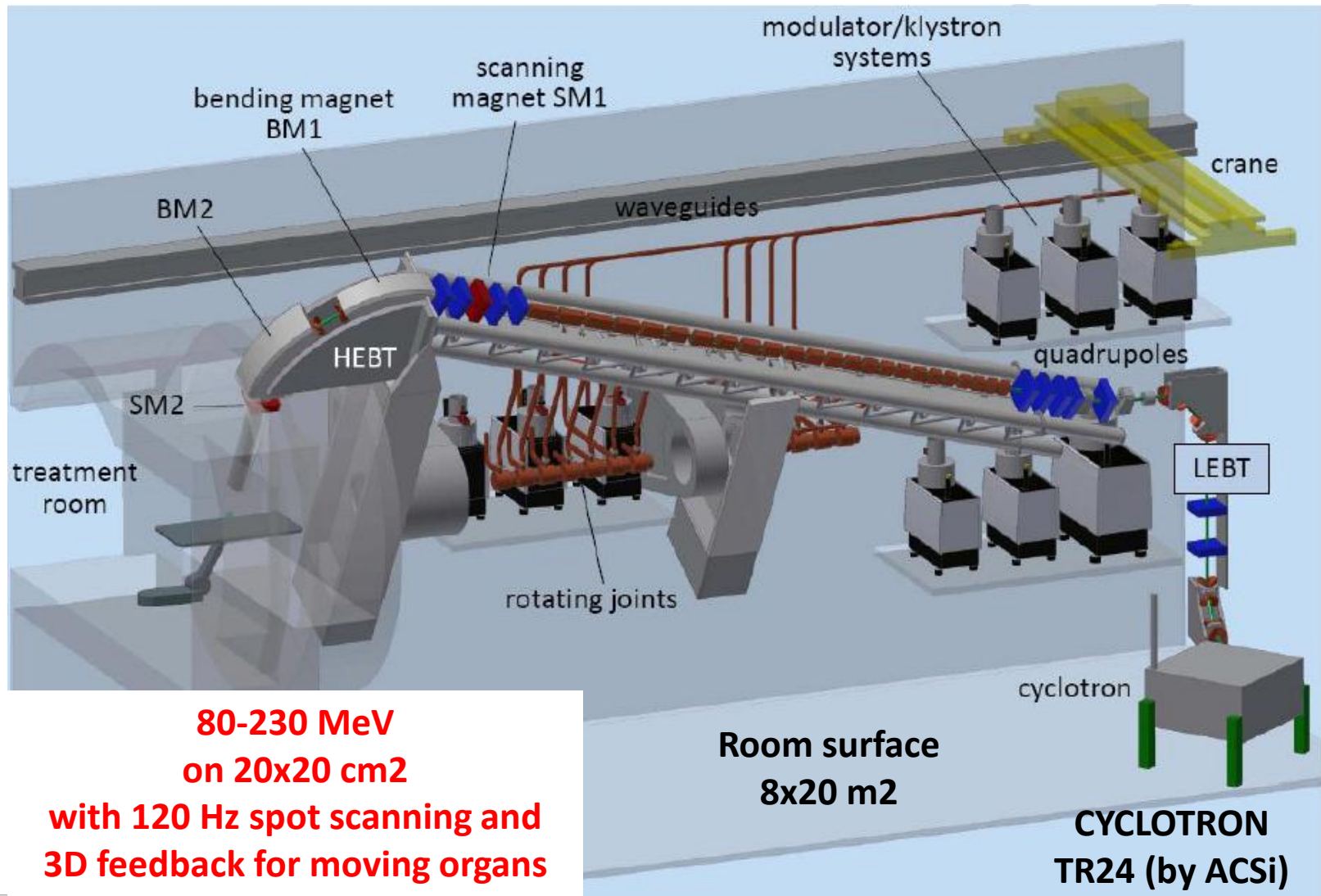
Monarch 250

25 M€

Single room facility by IBA

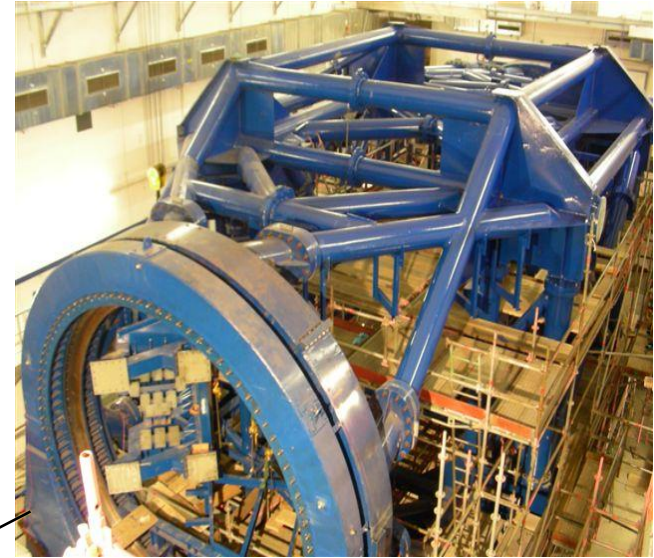


Single room facility by TERA: TULIP

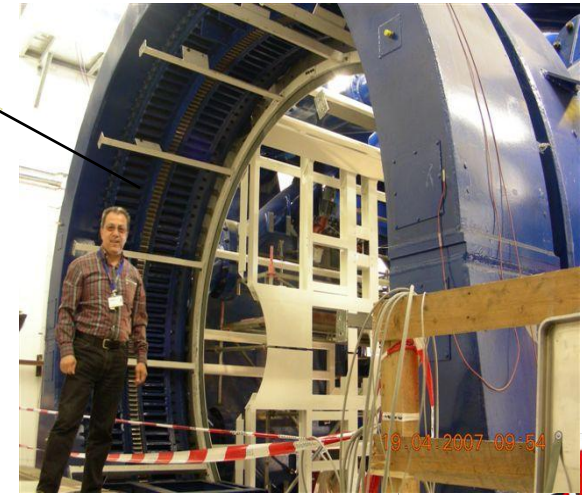
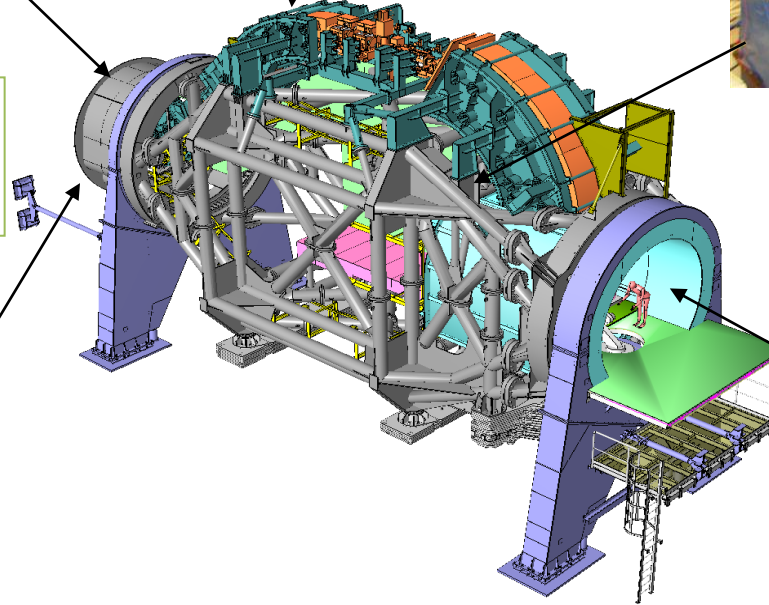


**80-230 MeV
on 20x20 cm²
with 120 Hz spot scanning and
3D feedback for moving organs**

Heidelberg ion gantry: 600 tons and 400 kW

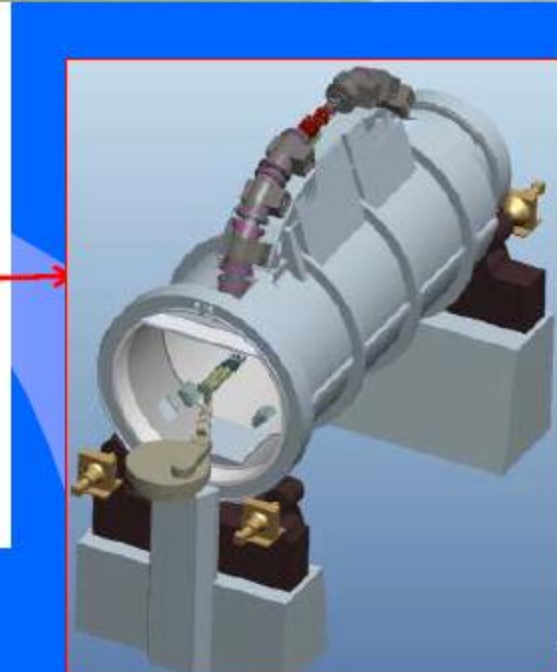
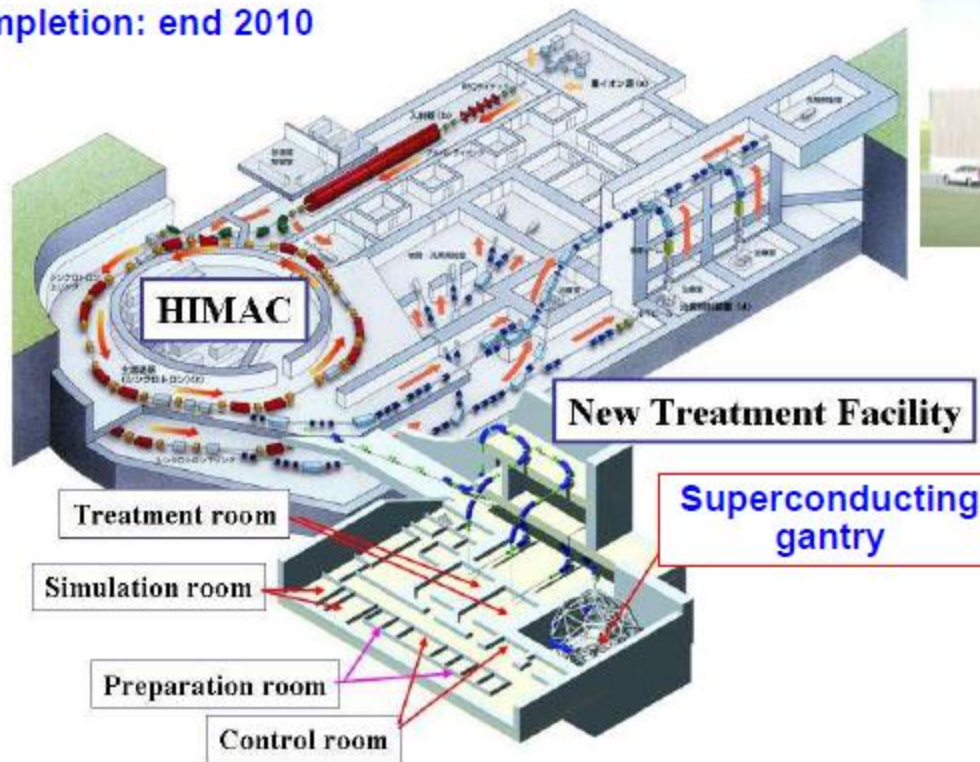


1st Rotation at
21.04.2007



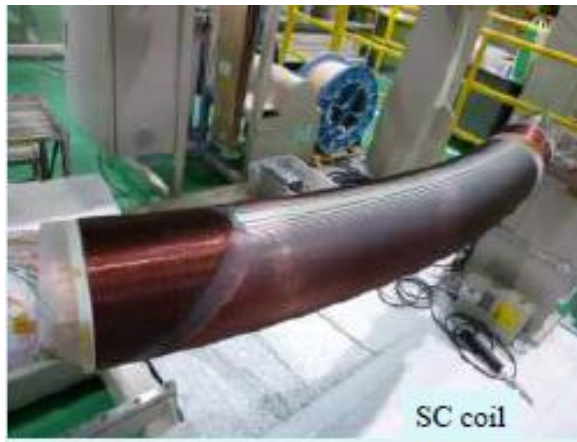
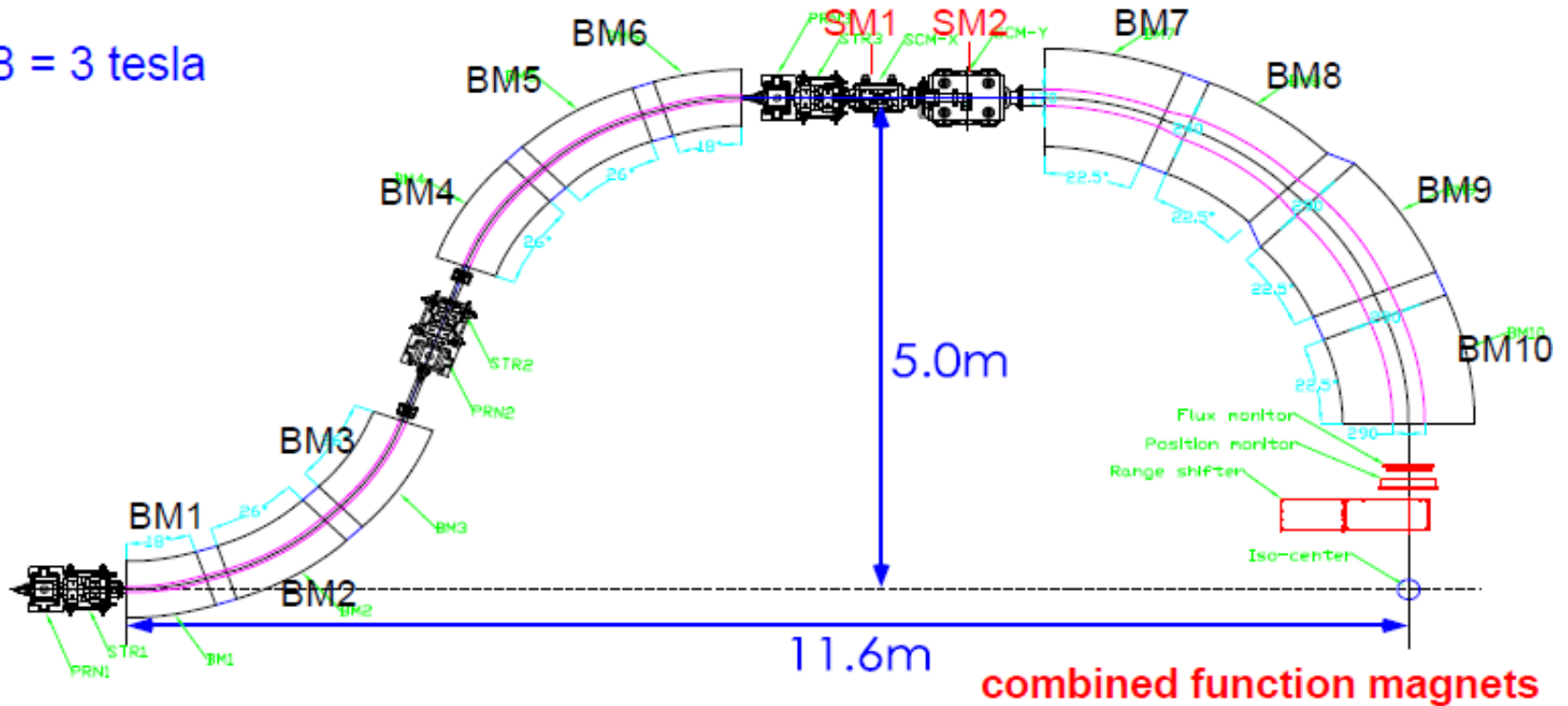
Gantries for carbon ion – Himac new facility

Completion: end 2010

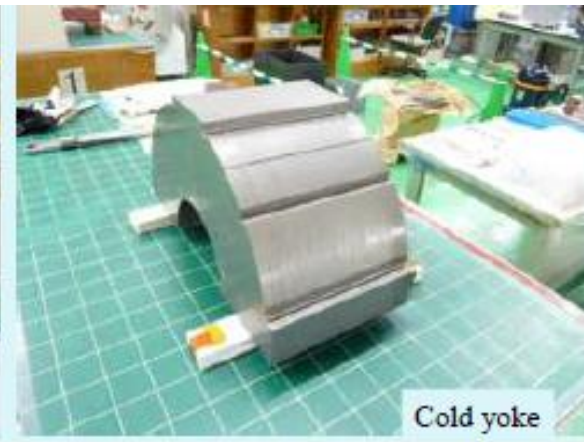


HIMAC superconducting gantry is in construction

B = 3 tesla

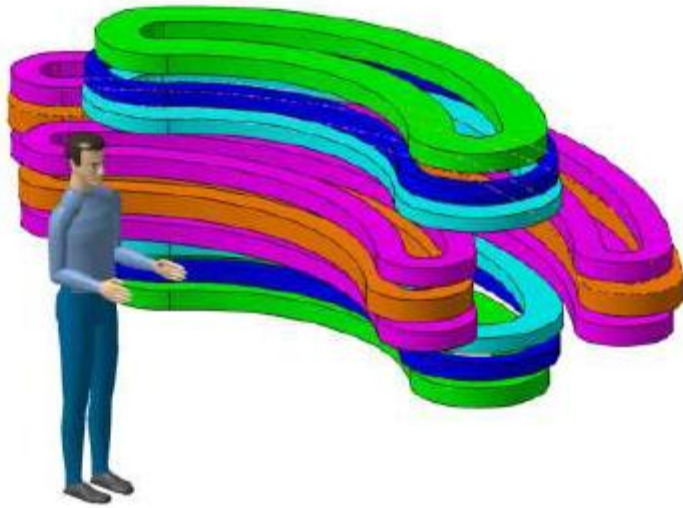


SC coil



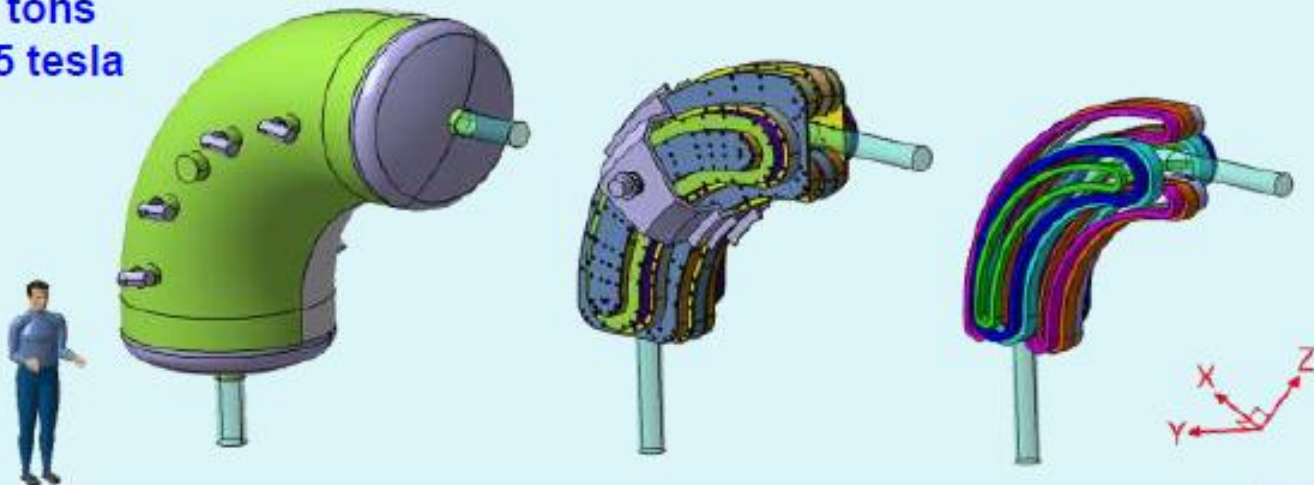
Cold yoke

Project by CEA (France) in collaboration with IBA



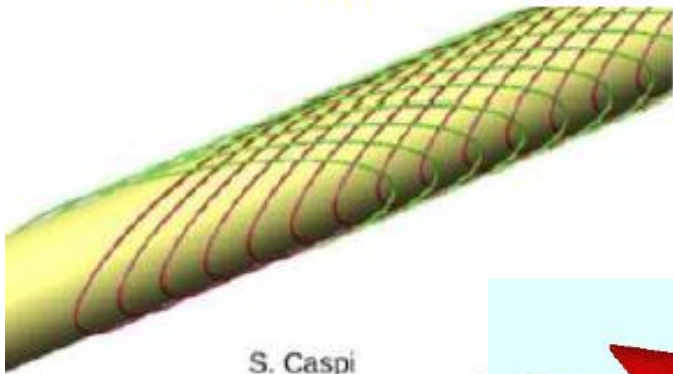
90° magnet following a design by INFN-Genoa and TERA

12.2 tons
 $B = 5$ tesla

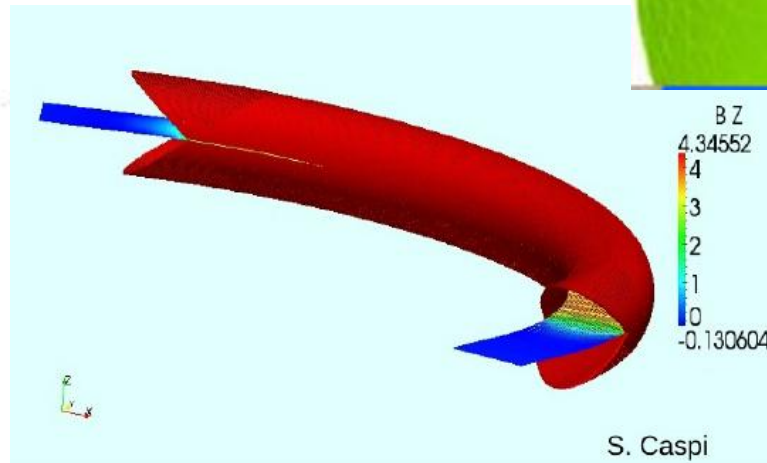
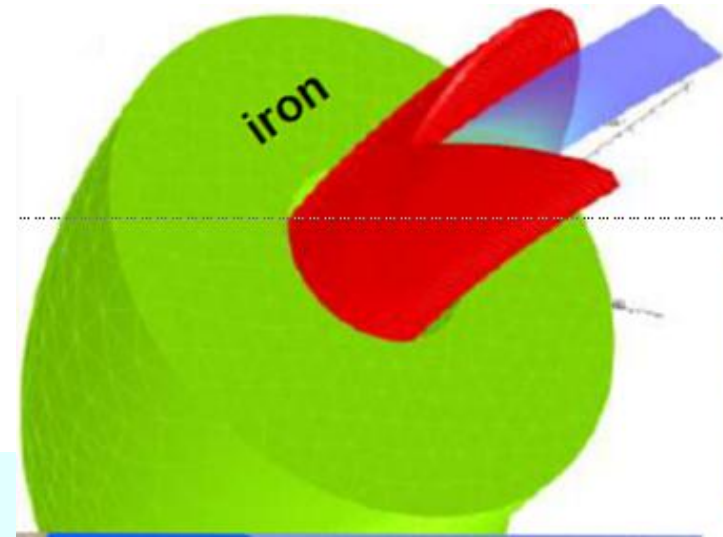


Work in progress at LBL - Berkley

Two layer helical wires on a straight cylinder give a dipole field



S. Caspi

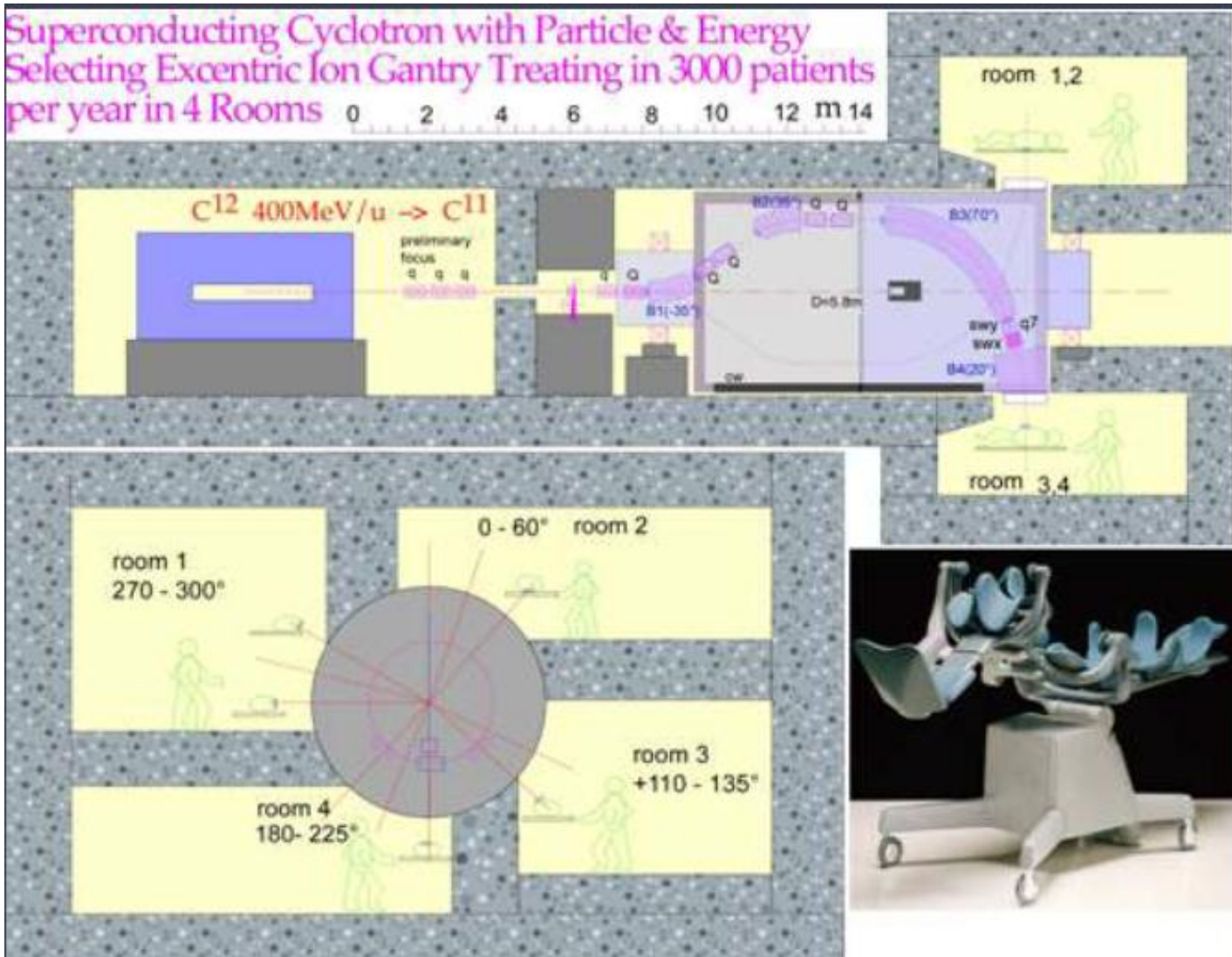


S. Caspi

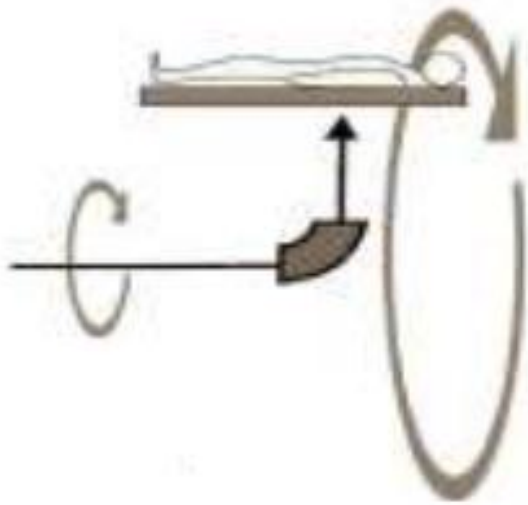
Shlomo Caspi, David Robin, Andy Sessler, Changchun Sun, Weishi Wan and Moohyun Yoon by LBNL LDRD funds

"Novel Design of Gantry Optics for Carbon Cancer Therapy Accelerator"

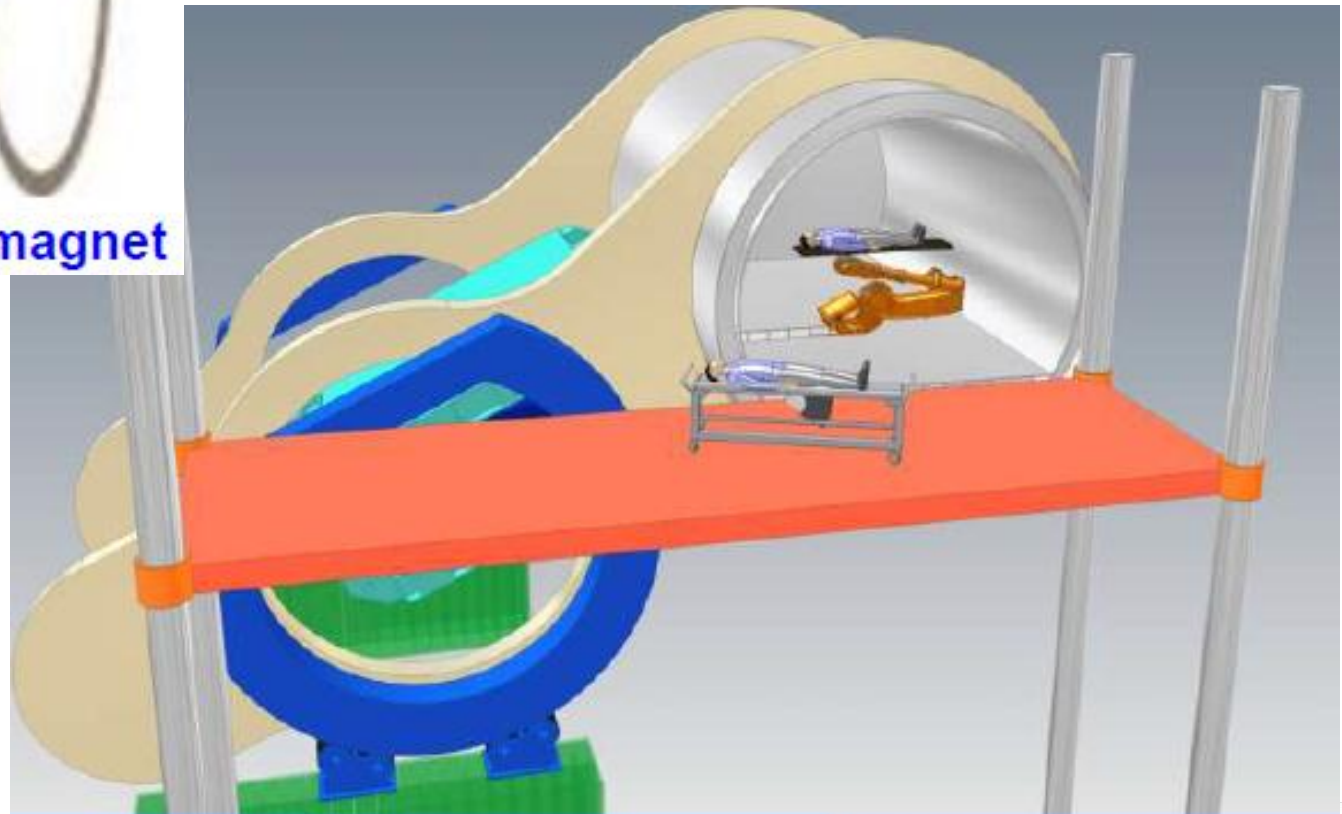
Many rooms gantry (A. Brahme – Stockholm)



'Riesenrad' gantry studied by Union of Light Ion Centres in Europe (ULICE – M. Pullia WP leader)



90° bending magnet



Summary 2nd part

Accelerators and technology for hadrontherapy : Status and future perspective

- ***Hadrontherapy is booming worldwide***
 - > 50 centers in the next few years
- ***Circular machines for hadrontherapy***
 - time characteristics of the beam
 - treatment modalities (passive spreading vs. active scanning)
- ***Future challenges in hadrontherapy***
 - Treatment of moving organs
 - Compact and cost effective machines (single room facilities and gantries)
- ***New technologies are under development (see ref.)***
 - Cyclinacs
 - Fixed Field Accelerating Gradients (FFAG)
 - Laser-plasma accelerators
 - Dielectric Wall Accelerators (DWA)
 - Superconducting magnets for carbon ion gantries

Conclusion

Conclusion

➤ ***Hadrontherapy is booming worldwide***

- ~ 30 centres in operation
- same number under construction

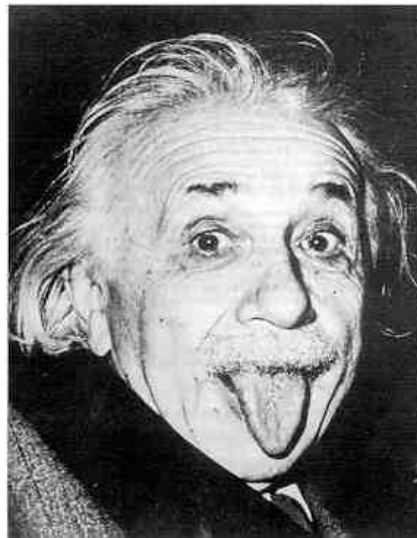
➤ ***Hadrontherapy is a multidisciplinary research field***

- physics (not only accelerators, also detectors for diagnostics!)
- radiobiology
- engineering
- clinical trials
- IT technology (GRID for hadrontherapy centres)

➤ ***New developments are needed***

- improve treatment modalities
- reduce size and cost of the machines!

Questions ???



THANK YOU for your ATTENTION!

General Summary

- What is the main difference between **protons** and **photons** in terms of dose deposition?
- Why **carbon ions** are '*qualitatively*' better than photons ?
- How the **therapeutic window** can be increased ?
- How many **patients per year** undergo radiotherapy/hadrontherapy treatments ?
- What is the typical **cost** of a multi-room hadrontherapy centre ?
- Where are most of the dual centers for hadrontherapy concentrated ?
- What are two of the main **challenges of hadrontherapy** ?
- What are the **beam characteristics** needed for proton therapy with active scanning techniques?
 - beam currents /energies?
 - beam time characteristics ?
- What does **cyclinac** mean ?

General Summary

- Protons have finite range in matter and the dose deposition is concentrated in the **Bragg peak**, while photons show an exponential depth dose profile.
- Carbon ions are densely ionizing radiations and produce not reparable **multiple close-by double strand breaks** in the DNA of the tumoral cells.
- By a better **dose conformity**, by the **fractionation** of the treatment, etc.
- In developed countries about 20,000 patients/year every 10 Million inhabitants undergo radiotherapy. About 12-15% of them would benefit from proton and carbon ion treatments (**paediatric tumours, radioresistant tumours**).
- A multi-room centre for hadrontherapy costs about **150-180 MEUR**. The accelerator counts for about 20% of the total cost.
- Japan is the best equipped country in terms of dual centres.
- Two of the main challenges of hadrontherapy are the treatment of **moving organs** and the development of compact accelerators for **single room facilities**.
- Typical beam for proton therapy should have a variable energy between **70-230 MeV** and average currents up to **1 nA**. A fast active energy variation in few ms timescale is best suited for the treatment of moving organs.
- The cyclinac is the combination of a cyclotron (used as injector) and a linear accelerator (used as booster).

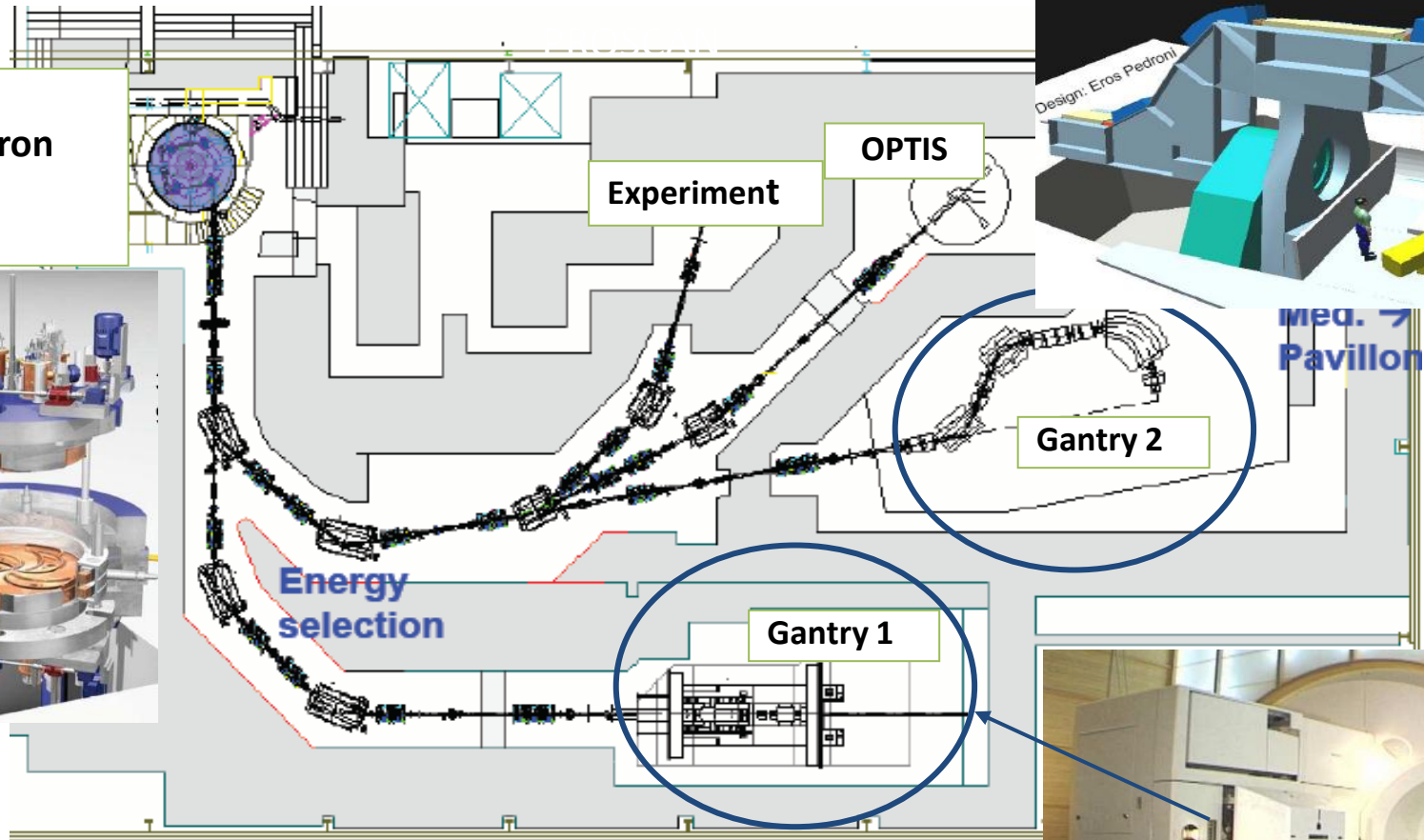
References

- R. R. Wilson, *Radiological use of fast protons*, *Radiology* 1946, 47: 487-491
- U. Amaldi, *Cancer therapy with particle accelerators*, *Nucl. Phys. A654*, pp. 375c-399c, 1999
- G. Kraft, *Tumor therapy with heavy charged particles*, *Progress in Particle and Nuclear Physics*, Volume 45, Supplement 2, S473-S544, 2000
- U. Amaldi, G. Kraft, *Radiotherapy with beam of carbon ions*, *Rep. Prog. Phys.* 68, 1861-1882, 2005
- Particle Therapy Co-Operative Group (<http://ptcog.web.psi.ch/>)
- ENLIGHT++ (<http://enlight.web.cern.ch/enlight/cms/index.php?file=home>)
- Review of Accelerators Science and Technology – RAST II on "Medical Applications of Accelerators"
(<http://www.worldscinet.com/rast/02/0201/S17936268090201.html>)

Back-up material

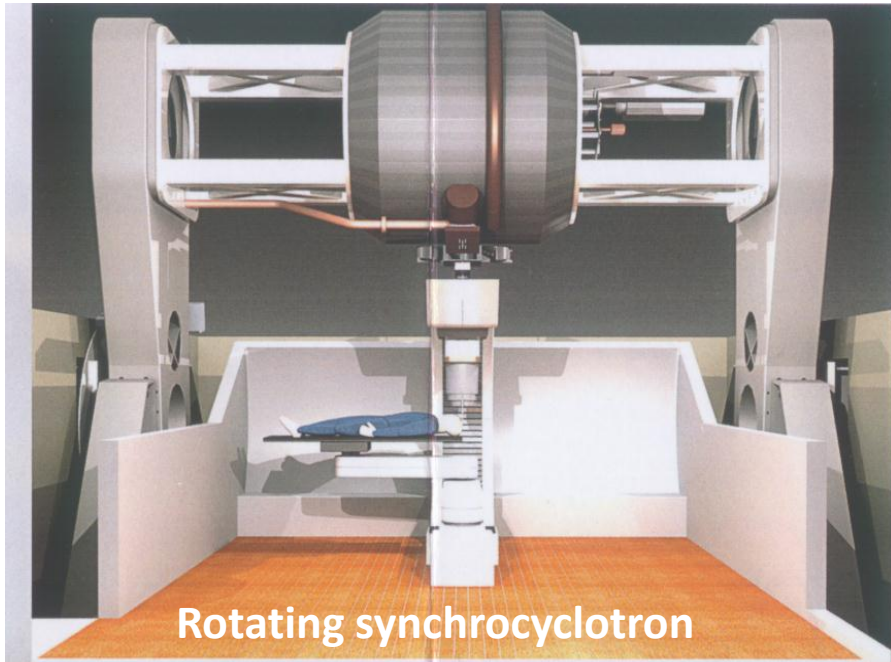
Two methods for imparting the dose: “passive” system and “active” scanning

ACCEL
SC cyclotron
250 MeV
protons

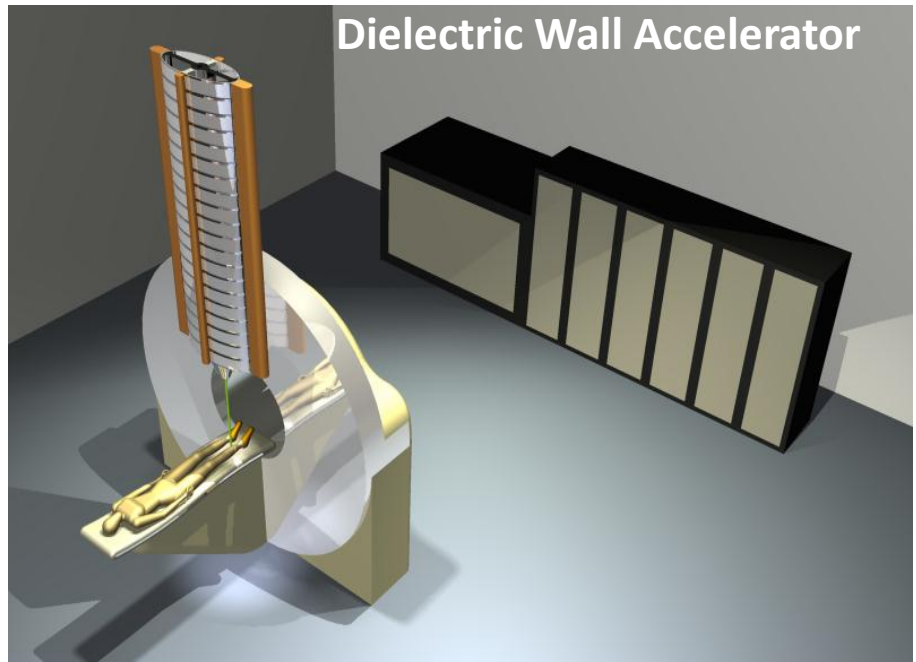


PROSCAN at PSI (Villigen):
with Gantry 1 and Gantry 2

Single room facilities: ongoing projects

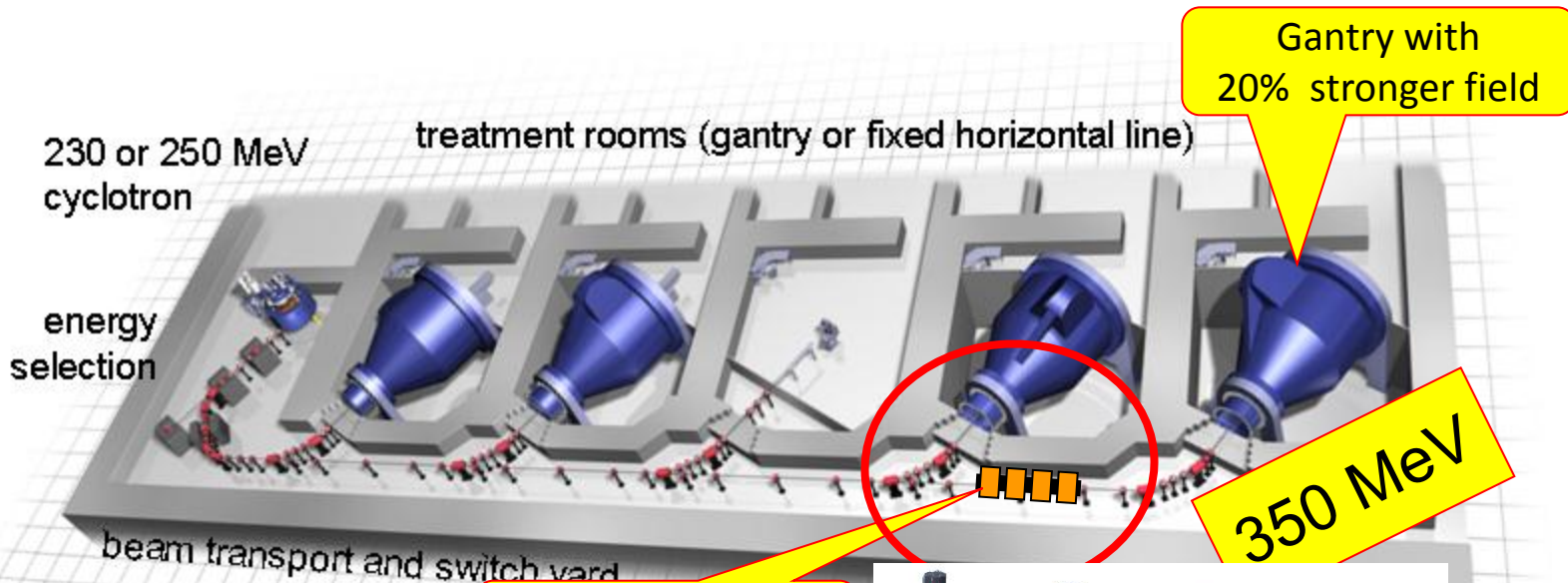


→ Still River Systems (Littleton, MA)



→ Los Alamos lab. (G. Caporaso et. al)
with CPAC.Co (Livermore,CA)

Upgrade for high energy



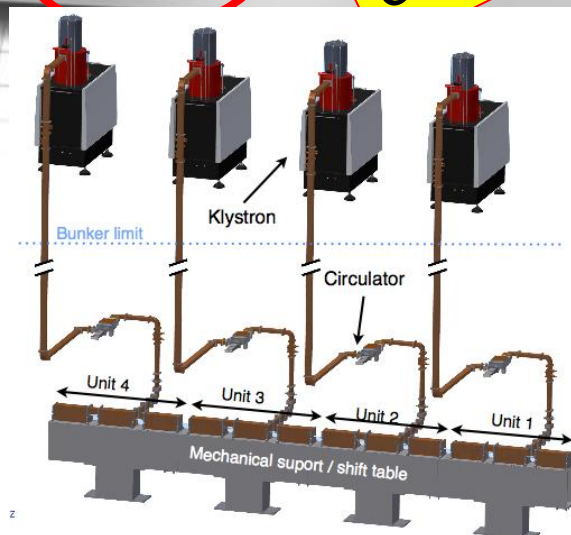
230 or 250 MeV

7m Linac

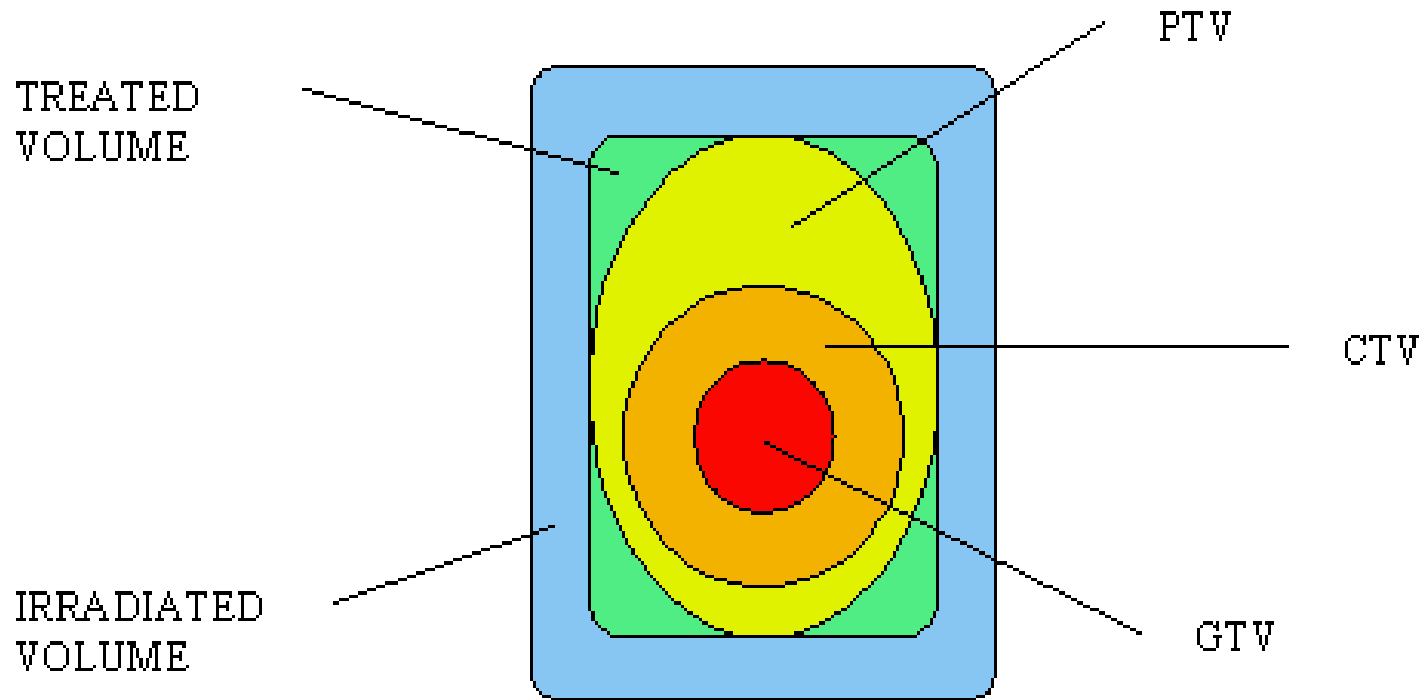
Linac based on existing TERA design of CCL linac

Gradient: 25 MV/m

=> 100 MeV needs effectively 7 m



The target volumes



GTV: Gross Target Volume as determined by CT, MRI, SPECT ad PET

CTV: the Clinical Target Volume takes into account invisible infiltrations

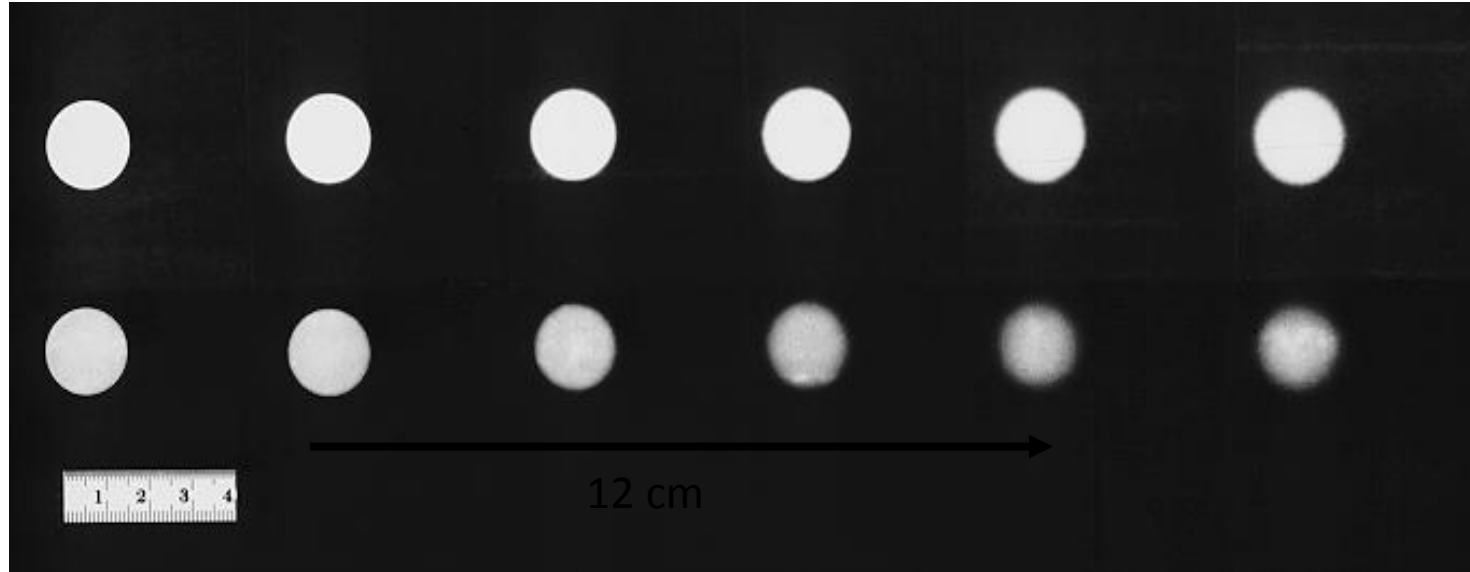
PTV: the Planning Treatment Volume takes into account mouvements and misalignments

CHALLENGE: Conform the dose to the tumour !

Carbon ions have less multiple scattering than protons : higher lateral precision

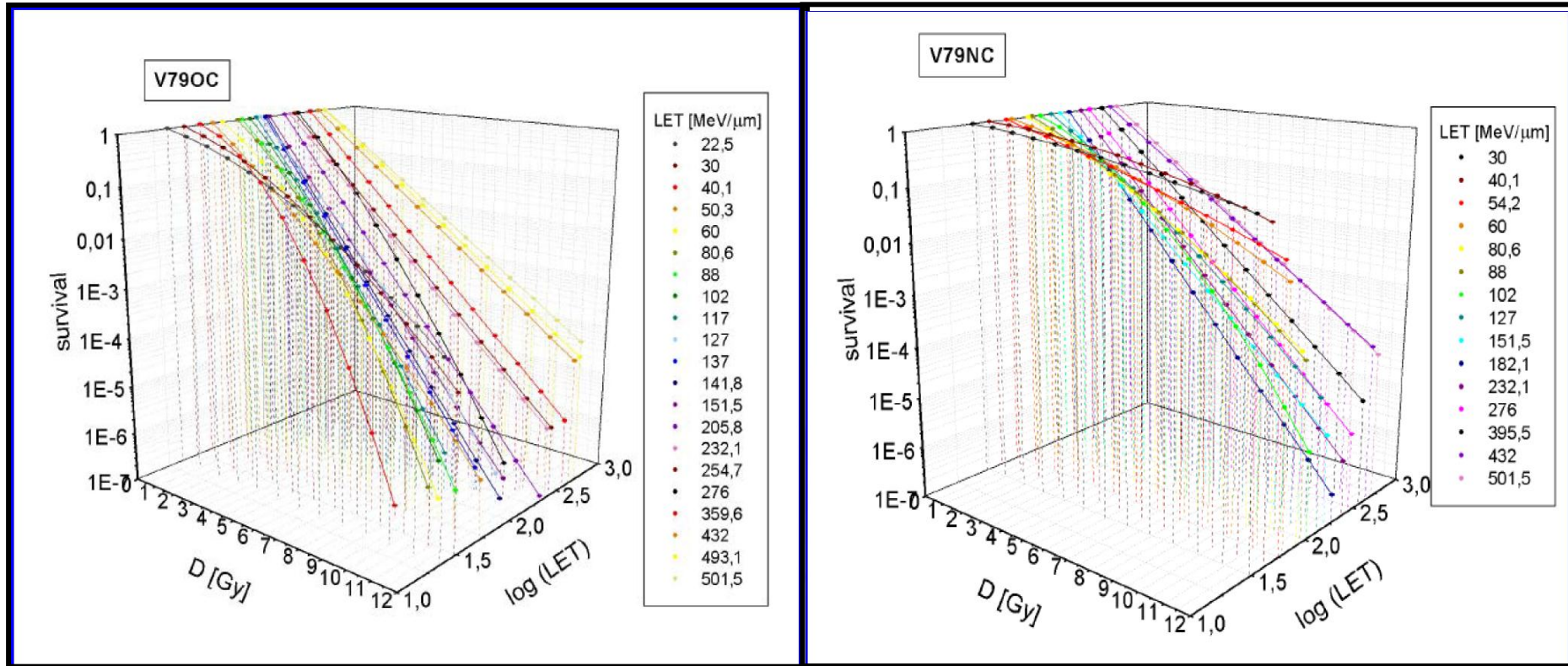
carbon beam

proton beam



Depth in tissue

Response of different cells to high-LET radiations

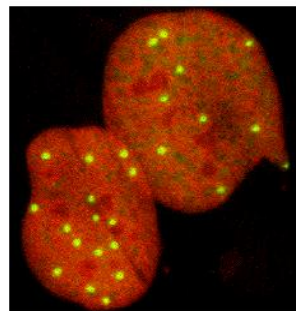
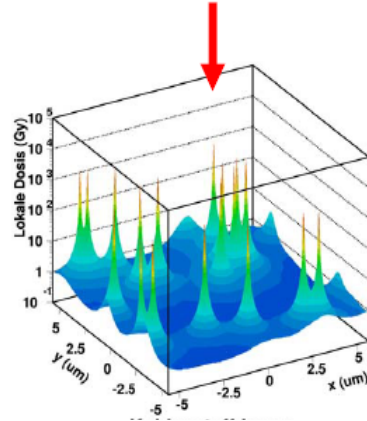
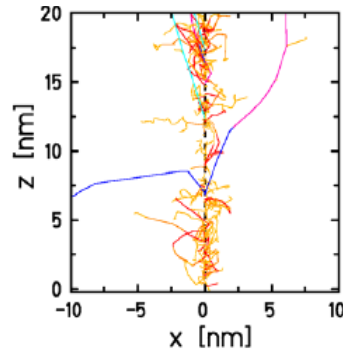


Survival of V79 aerated and anoxic cells versus LET of carbon-12 ions

Data: Furusawa *et al. Radiat. Res.* **154**, 485-496 (2000)

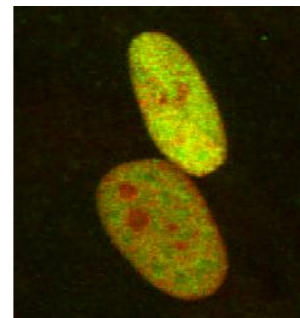
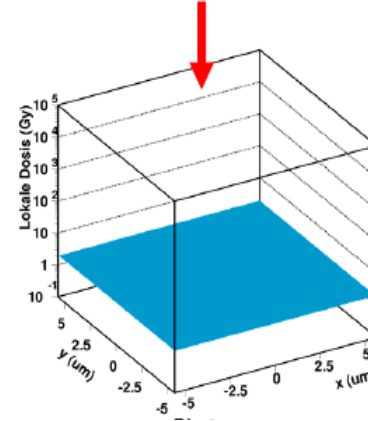
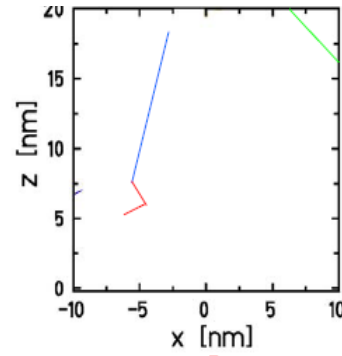
Two qualitatively different microscopic dose distributions

densely ionizing radiation



Visualization of repair proteins

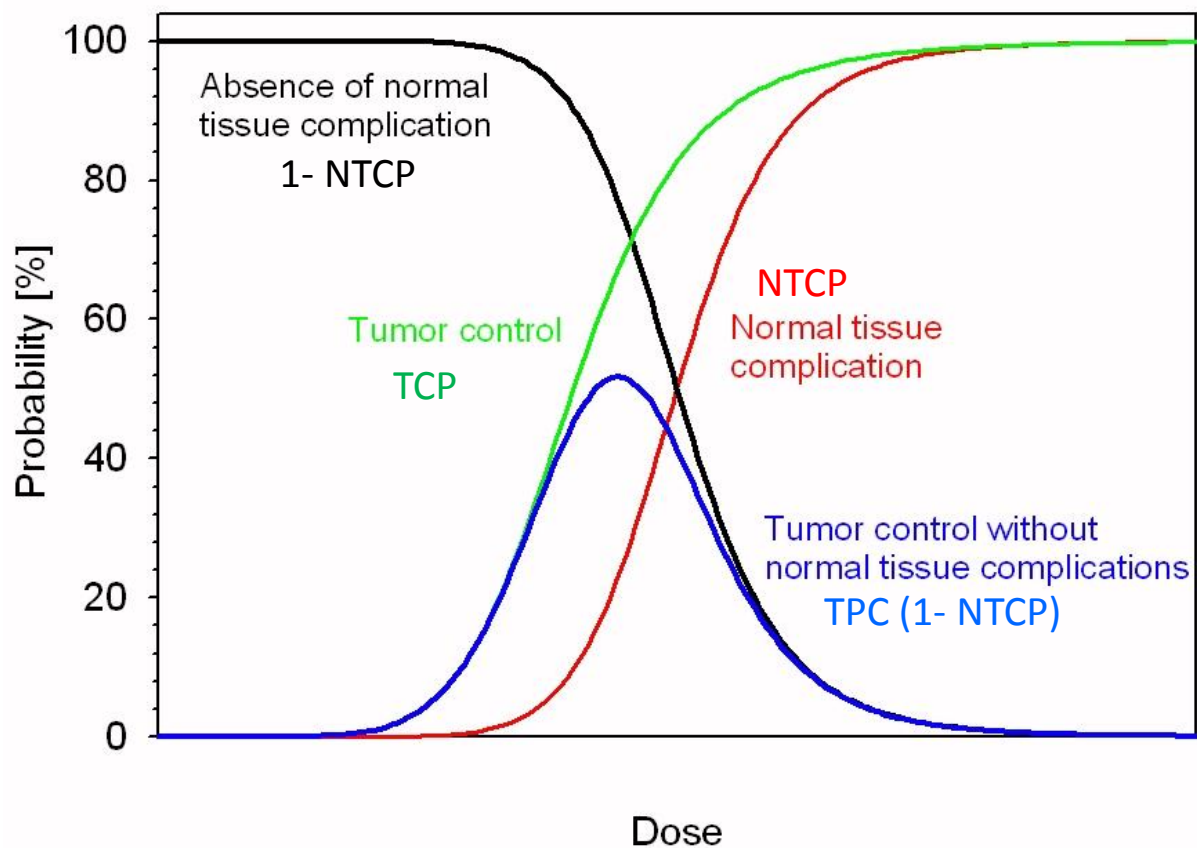
sparsely ionizing radiation



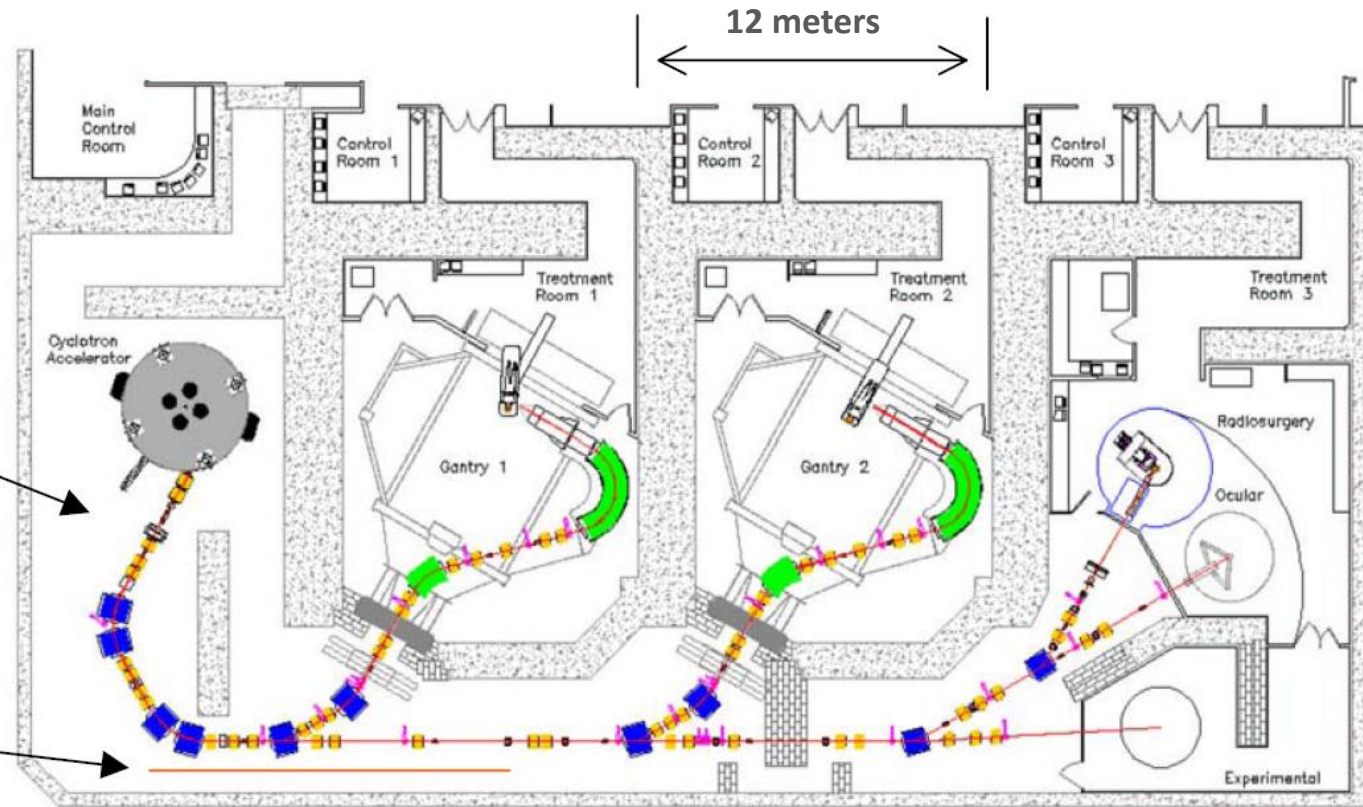
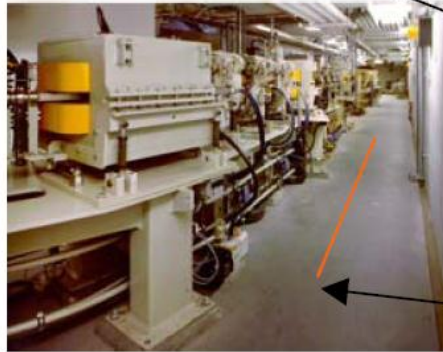
B. Jakob

GSI
M. Scholz

Quantification of the control without complications



Cyclotron solution for protons for MGH (Boston) by IBA



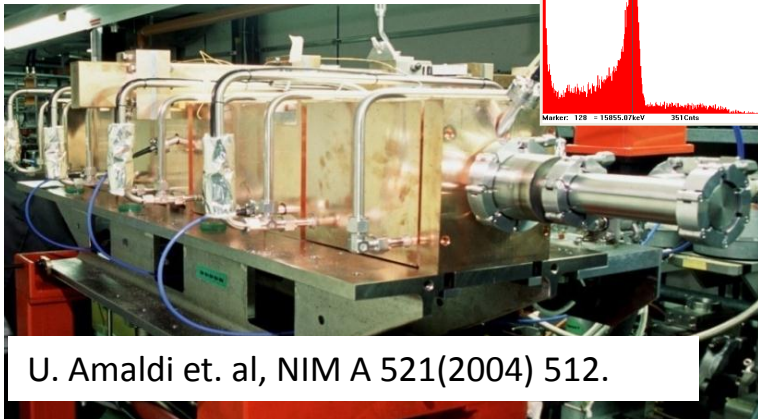
The Cyclinac solution

1993: first Cyclinac proposal

2001: first IDRA-design

2003: test on LIBO-62 MeV (TERA-CERN-INFN)

2009-2010: First Unit of LIGHT (A.D.A.M.=Application of Detectors and Accelerators to Medicine)

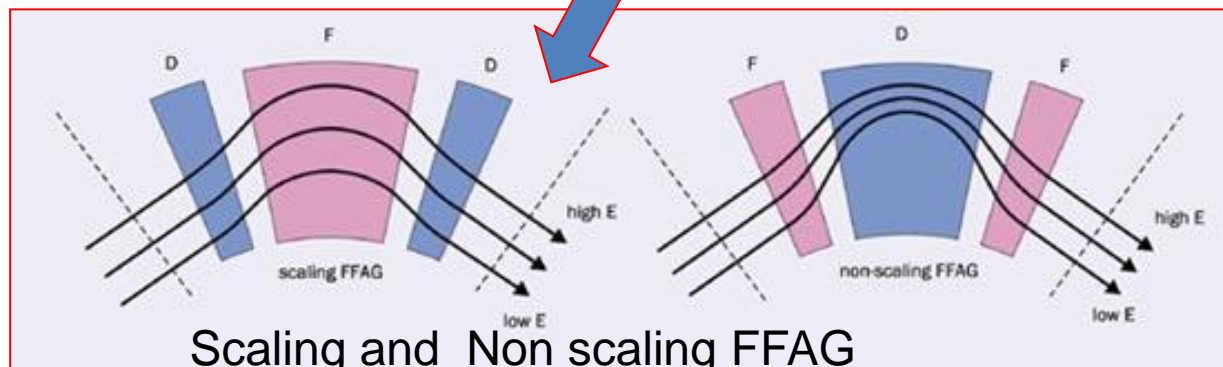
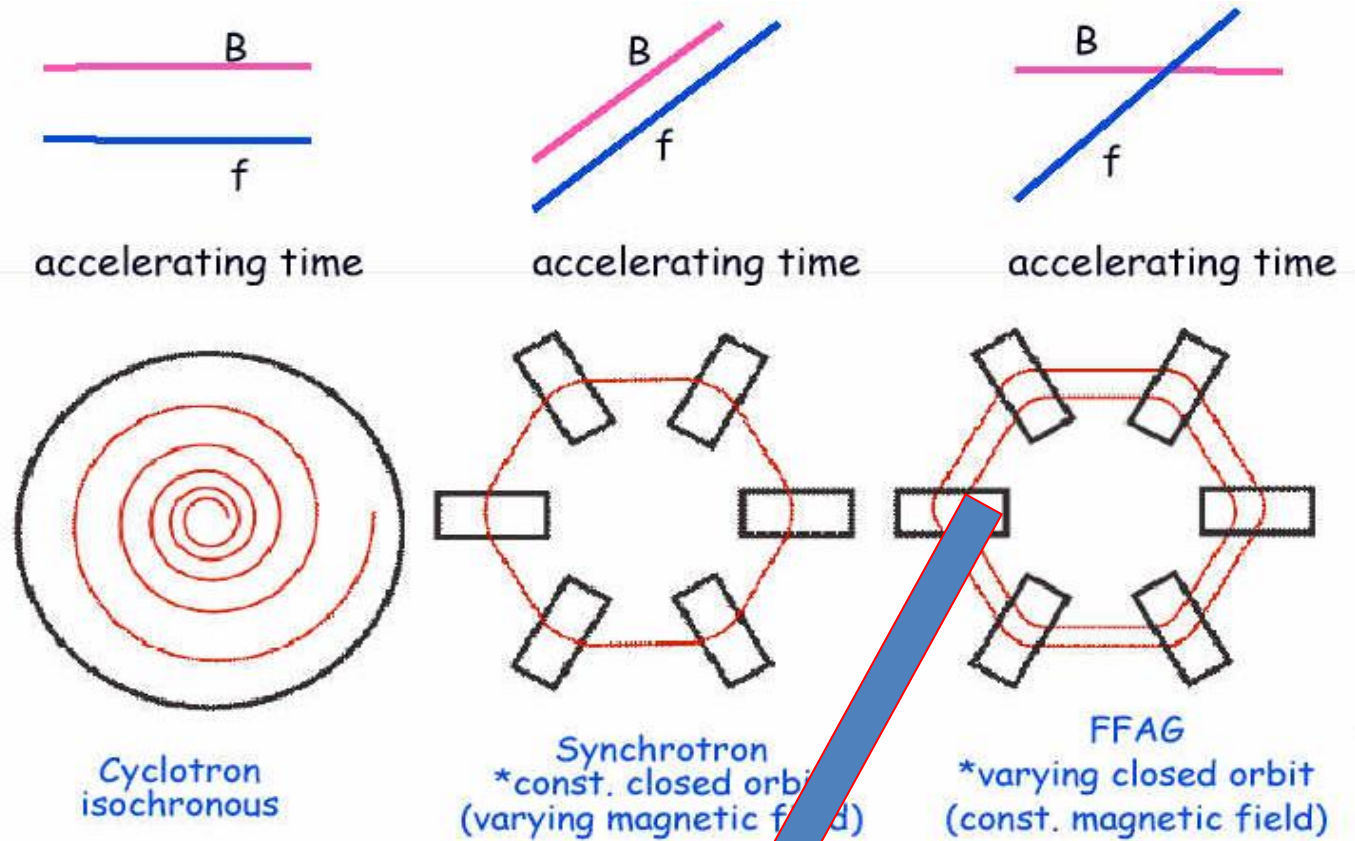


U. Amaldi et. al, NIM A 521(2004) 512.



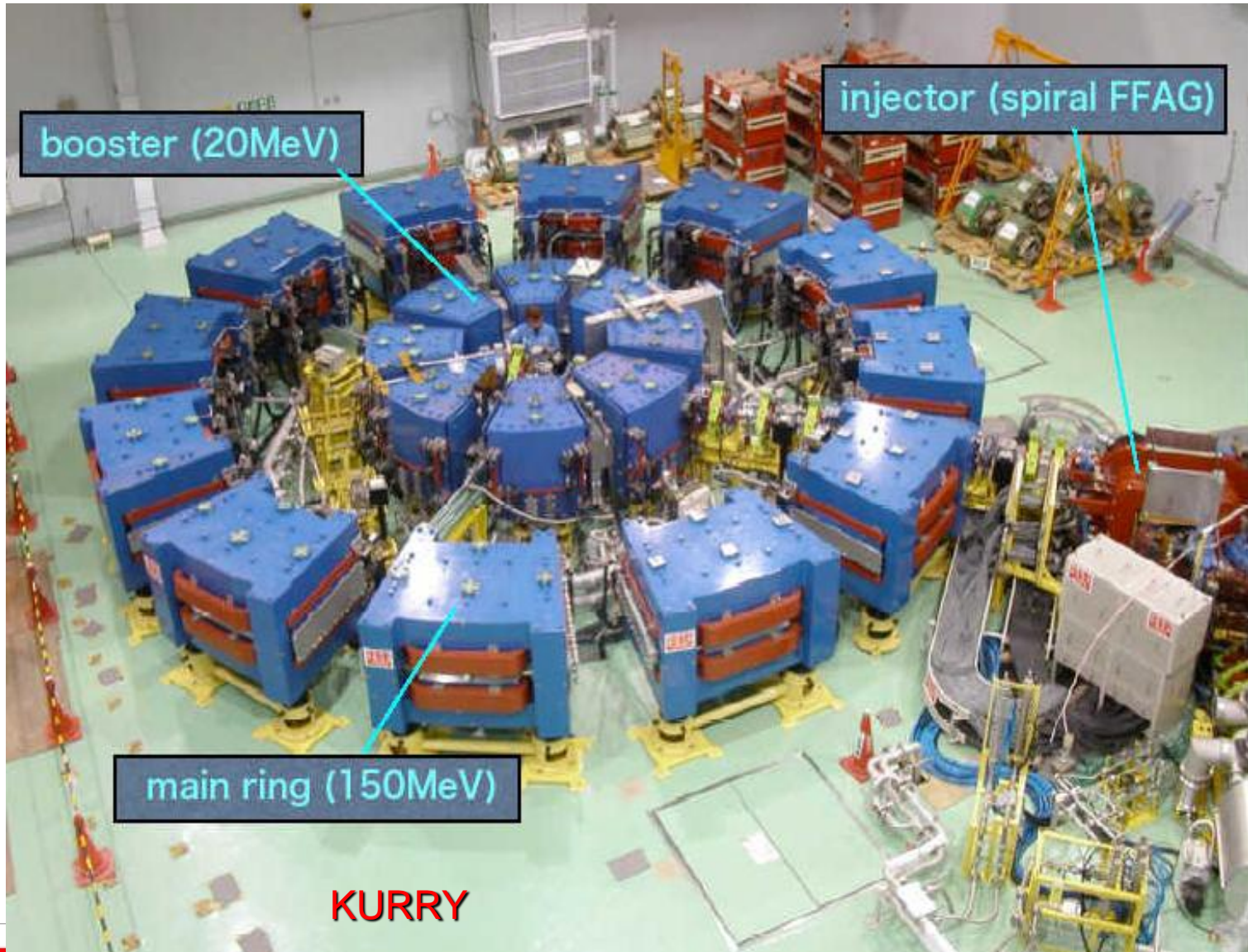
LIGHT = Linac for Image Guided Hadron Therapy

An old-new solution: Fixed Field Alternating Gradient



Scaling and Non scaling FFAG

The Japanese scaling 150 MeV proton FFAG



A non-scaling Fixed Field Alternating Gradient

DESIGN OF A NON-SCALING FFAG ACCELERATOR FOR PROTON THERAPY*

D. Trbojevic, A. G. Ruggiero, BNL, Upton, NY, USA, E Keil, CERN, Geneva, Switzerland, N. Neskovic, Vinca, Belgrade, and A. Sessler, LBL, Berkeley, CA, USA

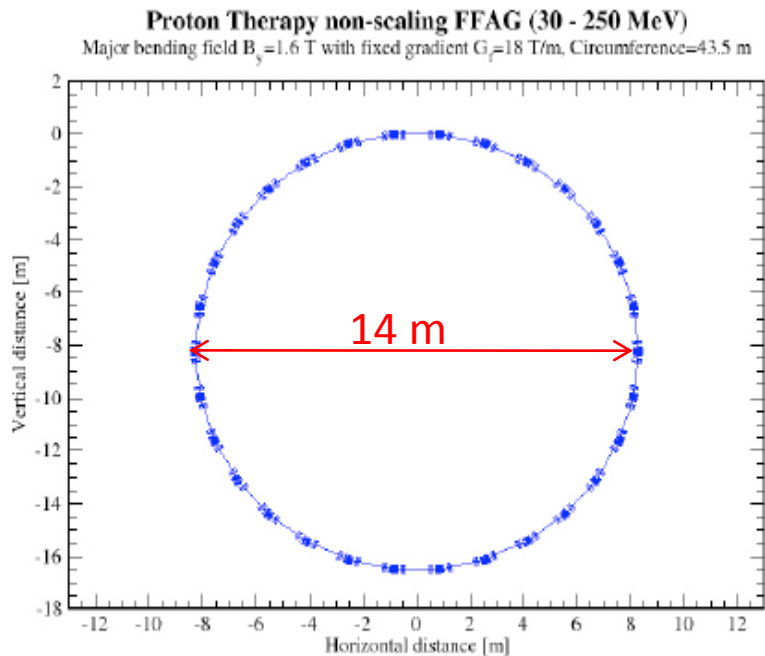


Figure 2. The whole ring of the fixed gradient lattice with 35 cells, $C=43.5$ m.

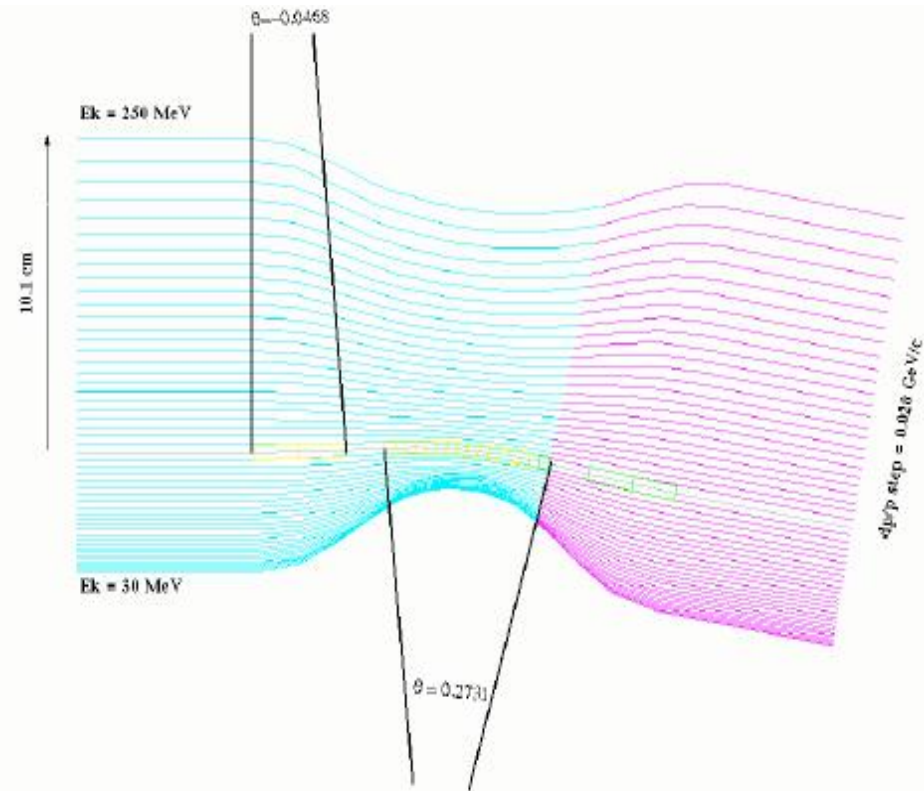
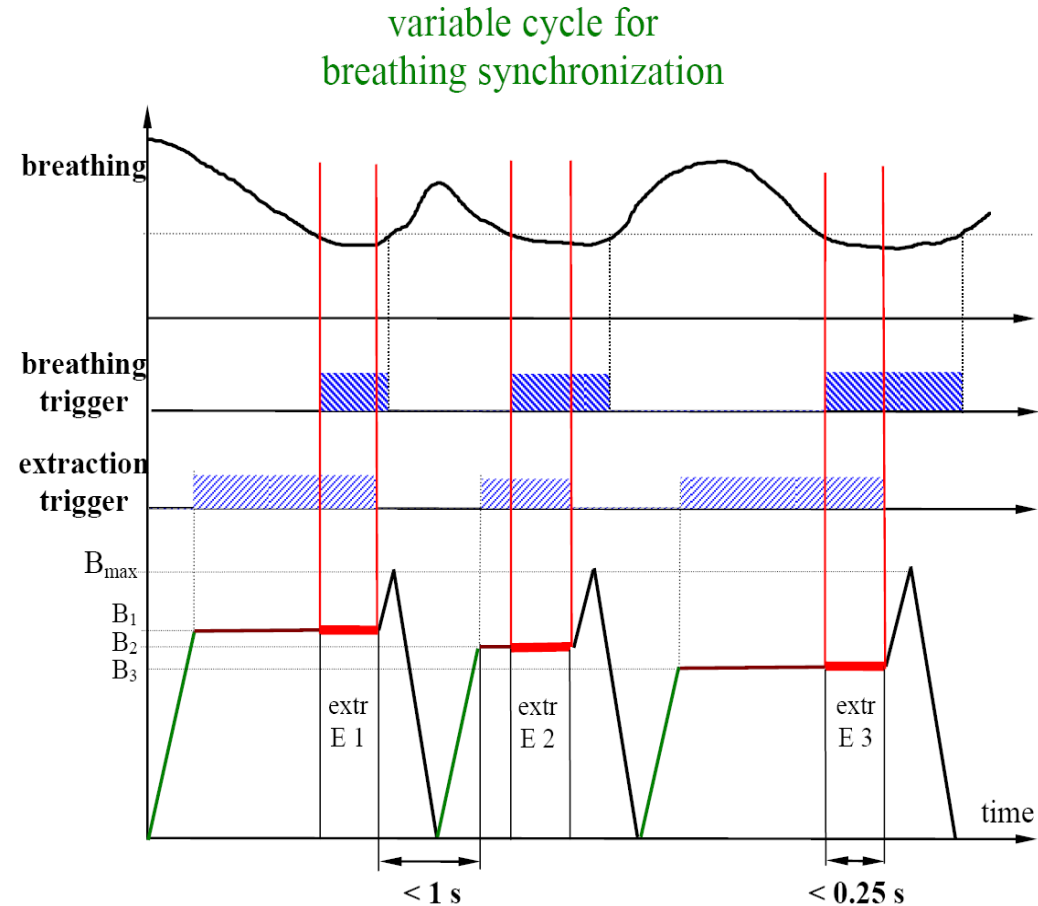


Figure 3. Orbits of particles during acceleration.

Treating moving organs

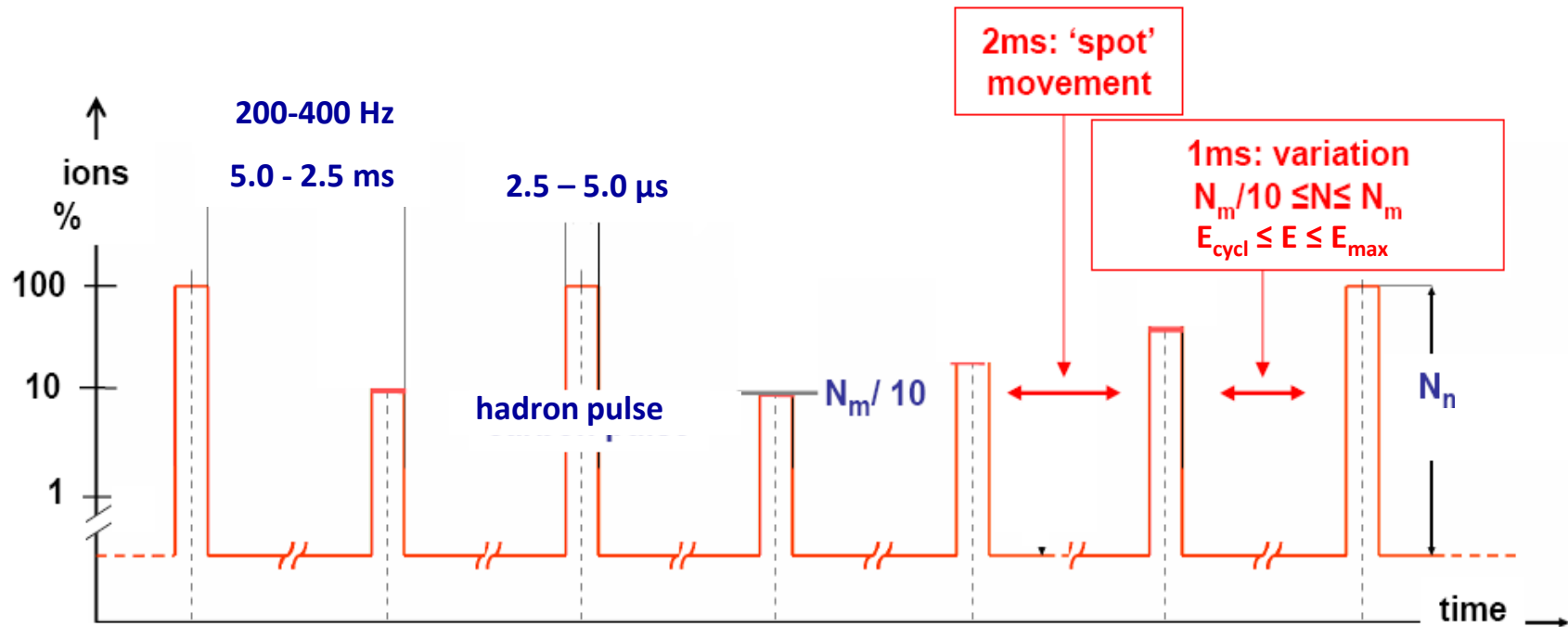
1. Respiratory gating with a synchrotron

- The beam reaches the patient only when the Target “gate” is ON
- Synchrotrons: synchronization of the respiration of the patient with the cycle of the accelerator
- Technique already in use in Japan (Tsukuba)



Cyclotrons are better because the beam is always present

The cyclinac beam is ideal for spot-scanning with many paintings and position feedbacks



The number of hadrons N , the two transverse positions and the depth of the spot can be varied every pulse, because the linac energy E can be adjusted every 1-2 ms