Seminar at the John Adams Institute for Accelerator Science
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Medical Applications of Particle Accelerators

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Particle accelerators operational in the world

Three main applications:

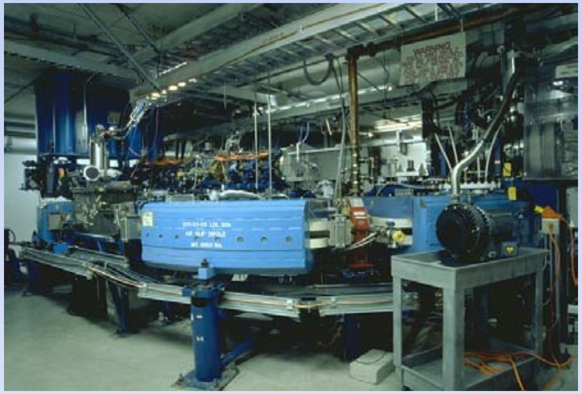
1) Scientific research
2) Medical applications
3) Industrial uses

CATEGORY OF ACCELERATORS	NUMBER IN USE (*)	
High-energy accelerators (E >1 GeV)	~ 120	
Synchrotron radiation sources	> 100	
Medical radioisotope production	~ 1,000	10,000
Accelerators for radiation therapy	> 7,500	
Research accelerators including biomedical research	~ 1,000	
Industrial processing and research	~ 1,500	
Ion implanters, surface modification	> 7,000	
TOTAL	> 18,000	

Adapted from "Maciszewski, W. and Scharf, W., *Particle accelerators for radiotherapy, Present status and future*, Physica Medica XX, 137-145 (2004)"

Particle accelerators for medical uses

- **Production of radionuclides with (low-energy) cyclotrons**
  - Imaging (PET and SPECT)
  - Therapy
- **Electron linacs for conventional radiation therapy, including advanced modalities**
- **Medium-energy cyclotrons and synchrotrons for hadron therapy with protons (250 MeV) or light ion beams (400 MeV/u ^{12}C-ions)**
  - Accelerators and beam delivery
  - New concepts



Radionuclide production

Radionuclide production

The use of radionuclides in the physical and biological sciences can be broken down into three general categories:

- Radiotracers
- Imaging (95% of medical uses)
  - SPECT (^{99m}Tc, ^{201}Tl, ^{123}I)
  - PET (^{11}C, ^{13}N, ^{15}O, ^{18}F)
- Therapy (5% of medical uses)
  - Brachytherapy (^{103}Pd)
  - Targeted therapy (^{211}At, ^{213}Bi)

Relevant physical parameters (function of the application)

- Type of emission (α, β^+, β^-, γ)
- Energy of emission
- Half-life
- Radiation dose (essentially determined by the parameters above)

Production methods

All radionuclides commonly administered to patients in nuclear medicine are *artificially* produced

Three production routes:

- (n, γ) reactions (**nuclear reactor**): the resulting nuclide has the same chemical properties as those of the target nuclide
- Fission (**nuclear reactor**) followed by separation
- Charged particle induced reaction (**cyclotron**): the resulting nucleus is usually that of a different element

Reactor versus accelerator produced radionuclides

Reactor produced radionuclides

The fission process is a source of a number of widely used radioisotopes (^{90}Sr, ^{99}Mo, ^{131}I and ^{133}Xe)

Major drawbacks:

- large quantities of radioactive waste material generated
- large amounts of radionuclides produced, including other radioisotopes of the desired species (no carrier free, low specific activity)

Accelerator produced radionuclides

Advantages

- ***more favorable decay characteristics*** (particle emission, half-life, gamma rays, etc.) in comparison with reactor produced radioisotopes.
- ***high specific activities*** can be obtained through charged particle induced reactions, e.g. (p,xn) and (p,α), which result in the product being a different element than the target
- ***fewer radioisotopic impurities*** are produce by selecting the energy window for irradiation
- ***small amount of radioactive waste*** generated
- access to accelerators is much easier than to reactors

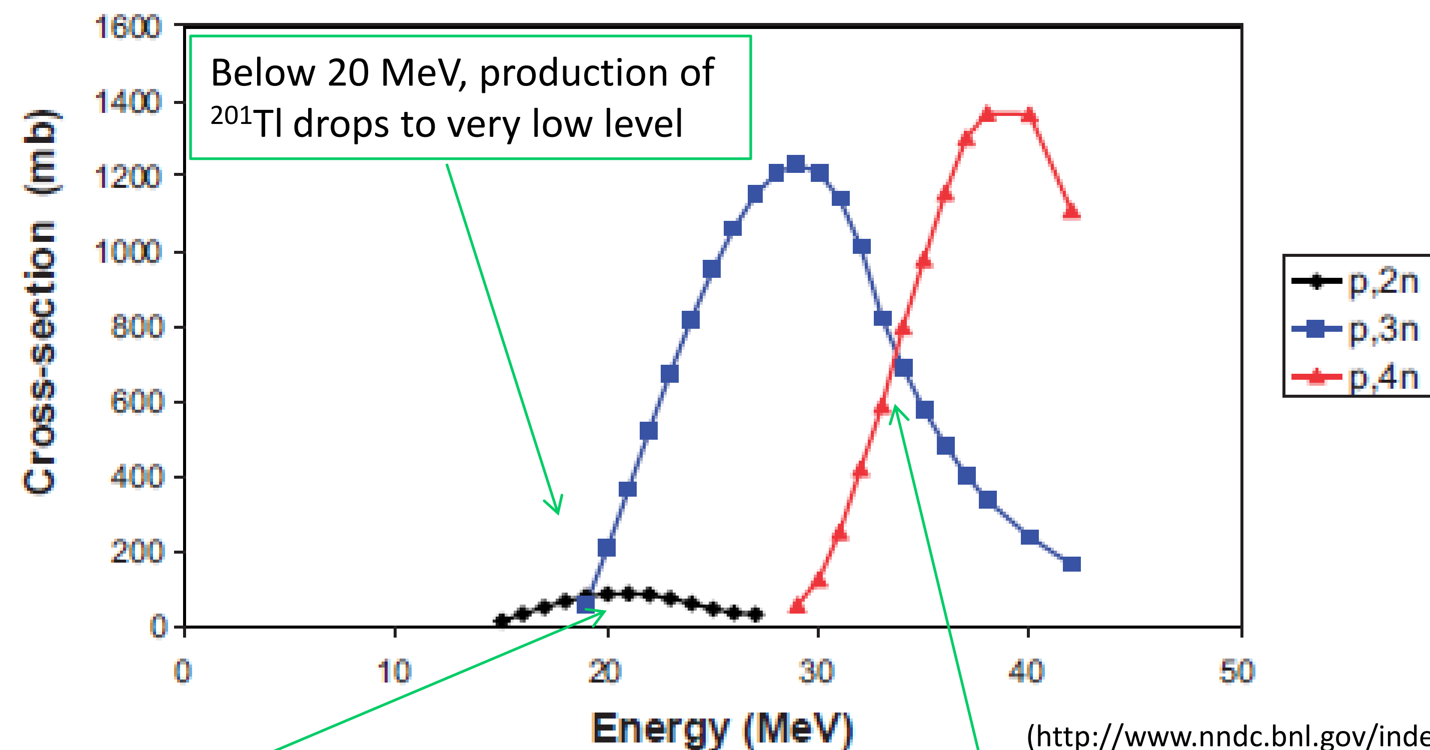
Major drawback: in some cases an enriched (and expensive) target material must be used

Tuning the beam energy, the example of ^{201}Tl

The nuclear reaction used for production of ^{201}Tl is the ^{203}Tl(p,3n)^{201}Pb

^{201}Pb ($T_{1/2}$ = 9.33 h) → ^{201}Tl ($T_{1/2}$ = 76.03 h)

Cross-section versus energy plot for the ^{203}Tl(p,2n)^{202}Pb, ^{203}Tl(p,3n)^{201}Pb and ^{203}Tl(p,4n)^{200}Pb reactions



Below 20 MeV, production of ^{201}Tl drops to very low level

Around threshold, production of ^{201}Tl is comparable to that of ^{202}Pb

Above 30 MeV, production of ^{200}Pb becomes significant

(http://www.nndc.bnl.gov/index.jsp)

Cyclotron-produced radionuclides for medical use

Most common radionuclides for medical use versus the proton energy required for their production

Four "reference" energy ranges

Proton energy (MeV)	Radionuclide easily produced
0 – 10	^{18}F, ^{15}O
11 – 16	^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{22}Na, ^{48}V
17 – 30	^{124}I, ^{123}I, ^{67}Ga, ^{111}In, ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{22}Na, ^{48}V, ^{201}Tl
≥ 30	^{124}I, ^{123}I, ^{67}Ga, ^{111}In, ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{82}Sr, ^{68}Ge, ^{22}Na, ^{48}V

IAEA Technical Report Series 465, Cyclotron produced radionuclides: principles and practice

Radionuclides for therapy

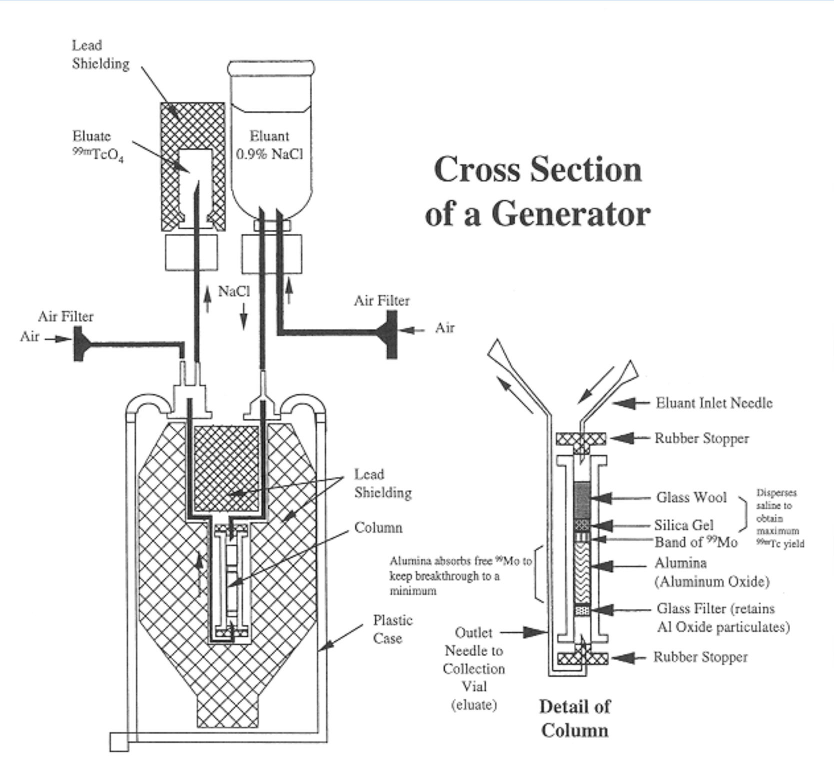
- High LET decay products (Auger electrons, beta particles or alpha particles)
- Radionuclide linked to a biologically active molecule that can be directed to a tumour site
- Beta emitting radionuclides are neutron rich ⟹ they are in general produced in reactors, *but* some interesting ones are better produced by accelerators

Radionuclide	Half-life	Decay mode	Reaction	Energy (MeV)
Br-77	2.4 d	Auger electrons	^{75}As(α, 2n)	27
			^{77}Se(p, n)	13
			^{78}Se(p, 2n)	24
			^{79,81}Br(p, xn)^{77}Kr	45
			^{nat}Mo(p, spall.)	>200
Pd-103	17.5 d	Auger electrons	^{103}Rh(p, n)	19
			^{nat}Ag(p, xn)	>70
Re-186	90.6 h	β^-	^{186}W(p, n)	18
			^{186}W(d, 2n)	20
			^{197}Au(p, spall.)	>200
			^{nat}Au(p, spall.)	>200
			^{nat}Ir(p, spall.)	>200
At-211	7.2 h	α	^{209}Bi(α, 2n)	28
			^{209}Bi(^{7}Li, 5n)^{211}Rn	60
			^{232}Th(p, spall.)^{211}Rn	>200

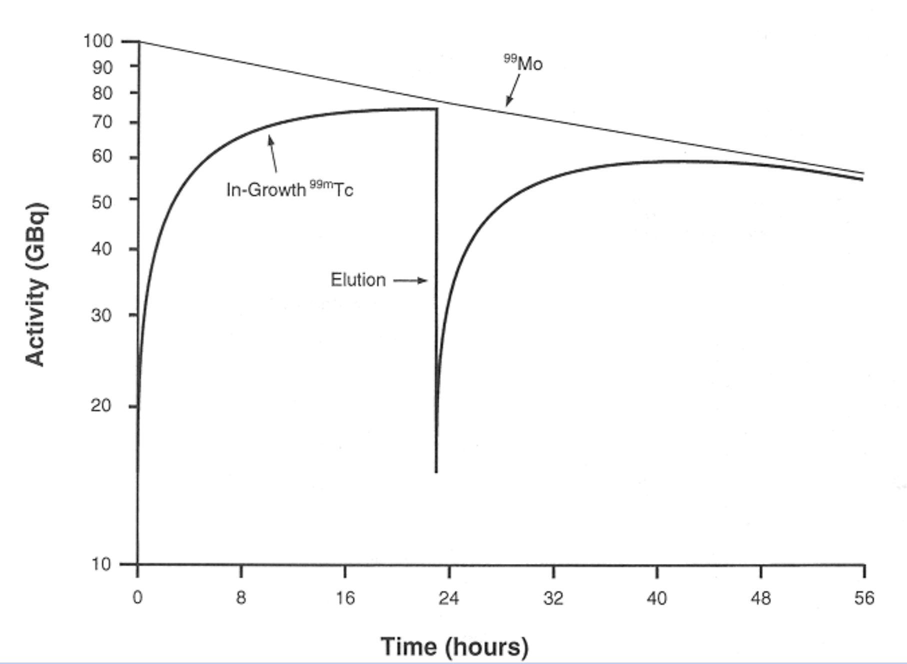
Radionuclide generators: $^{99}Mo/^{99m}Tc$

- Technetium-99m (^{99m}Tc) has been the most important radionuclide used in nuclear medicine
- Short half-life (6 hours)
- Supply problem overcome by obtaining parent ^{99}Mo, which has a longer half-life (67 hours) and continually produces ^{99m}Tc

- A system for holding the parent in such a way that the daughter can be easily separated for clinical use is called a *radionuclide generator*



^{99}Mo/^{99m}Tc generator



- Between elutions, the daughter (^{99m}Tc) builds up as the parent (^{99}Mo) continues to decay
- *Transient equilibrium* reached after approximately 23 hours
- Once transient equilibrium has been reached, the daughter activity decreases, with an apparent half-life equal to the half-life of the parent
- Transient equilibrium occurs when the half-life of the parent is greater than that of the daughter by a factor of about 10

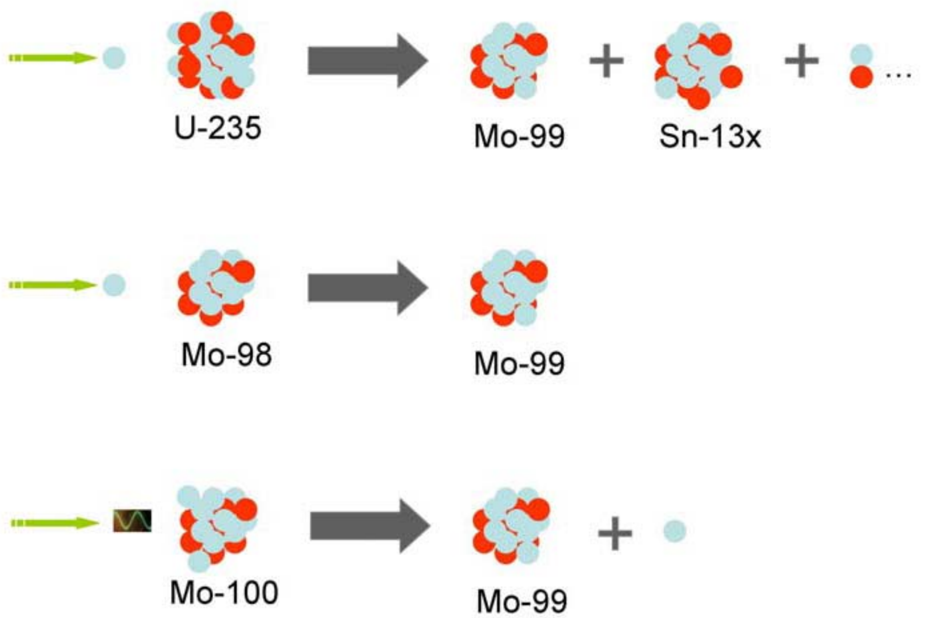
- **^{99m}Tc** labels hundreds of different molecular probes: more than 30 million medical protocols/year = 80% of all diagnostics procedures
- World requirement of ^{99}Mo: Europe represents approximately 22% of the total market, North America 52%, Asia / Pacific 20%, and other world regions 6%
- The worldwide supply chain of ^{99}Mo is essentially based on the activity of five research reactors

Accelerator-production of ^{99}Mo

Two alternative paths for the production of ^{99}Mo by accelerators

- Electron accelerator → Photo-fission
- Proton accelerator → Adiabatic Resonance Crossing (ARC)

Nuclear processes for producing ^{99}Mo



Neutron-fission of U-235 (present technique used in nuclear reactors)

Neutron-capture process (ARC method)

Photo-neutron process

High-power e⁻ accelerator → high-Z converter target → bremsstrahlung photons → ^{100}Mo target, ^{100}Mo(γ,n)^{99}Mo

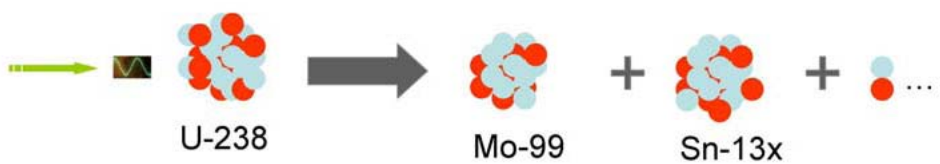


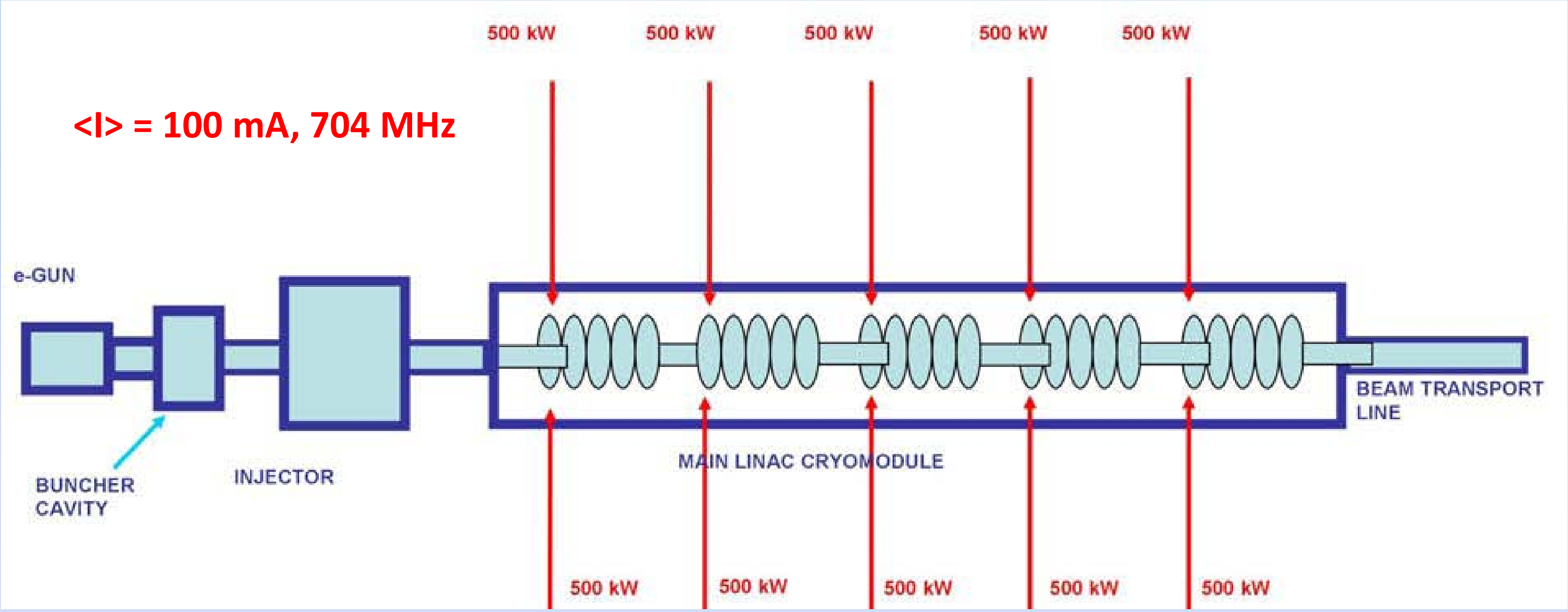
Photo-fission of U-238 (technique proposed by TRIUMF)

High-power e⁻ accelerator → ^{238}U target → bremsstrahlung photons → ^{238}U(γ,f)^{99}Mo

From "Making Medical Isotopes, *Report of the Task Force on Alternatives for Medical-Isotope Production,* TRIUMF, Canada (2008)"

Linac conceptual design

- **BNL-based design, 50 MeV, 100 mA = 5 MW beam power**
- **Superconducting RF accelerating structures operating at 704 MHz**
- **Single cryo-module housing five 5-cell cavities, each providing an energy gain of approximately 10 MeV**
- **Estimated cost 50 – 60 M Canadian $**
- **Construction timescale 3-4 years**



From “Making Medical Isotopes, *Report of the Task Force on Alternatives for Medical-Isotope Production,* TRIUMF, Canada (2008)”

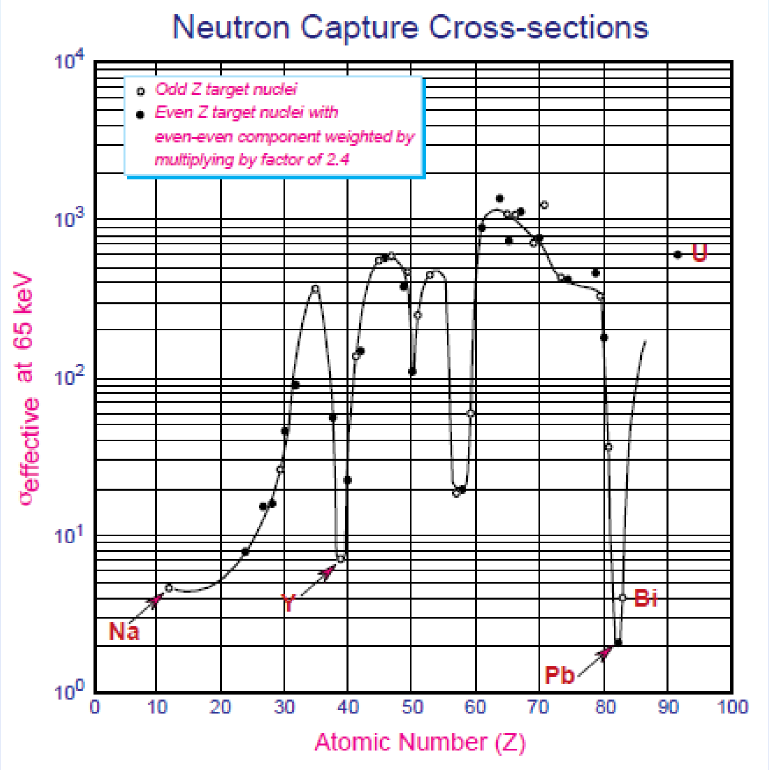
Adiabatic Resonance Crossing (ARC)

- Proposed by Physics Nobel Laureate Carlo Rubbia at CERN
  - ✓ C. Rubbia, Resonance enhanced neutron captures for element activation and waste transmutation, CERN-LHC/97-0040EET, 1997
- Tested at CERN for the transmutation of ^{99}Tc (TARC experiment)
  - ✓ TARC collaboration, Neutron-driven nuclear transmutation by adiabatic resonance crossing, CERN-SL-99-036EET, 1999

- Recently investigated for the production of ^{99}Mo via ^{98}Mo(n,γ) reaction at UCL (Belgium) and JRC Ispra (Italy)
  - ✓ P. Froment et al, The production of radioisotopes for medical applications by the adiabatic resonance crossing (ARC) technique, NIM A 493 (2002) p. 165 (also production of ^{125}Xe via the ^{124}(n,γ) capture reaction)
  - ✓ K. Abbas et al, Design and test of an accelerator driven neutron activator at the JRC cyclotron of the European Commission, Proc. Cyclotrons and Their Applications, 2007, 18th International Conference, p. 228

Adiabatic Resonance Crossing (ARC)

1. Lead has the lowest capture cross-section for non thermal neutrons ⟹ "transparent" to high-energy neutrons being moderated into it
2. Because lead is a heavy element, high-energy neutrons loose energy in very small steps
3. At each collision neutrons loose a constant fraction of energy in small steps ⟹ neutrons progressively "scan" the whole energy interval down to thermal energies, "seeking" the large values of the capture cross-section of the sample to be captured



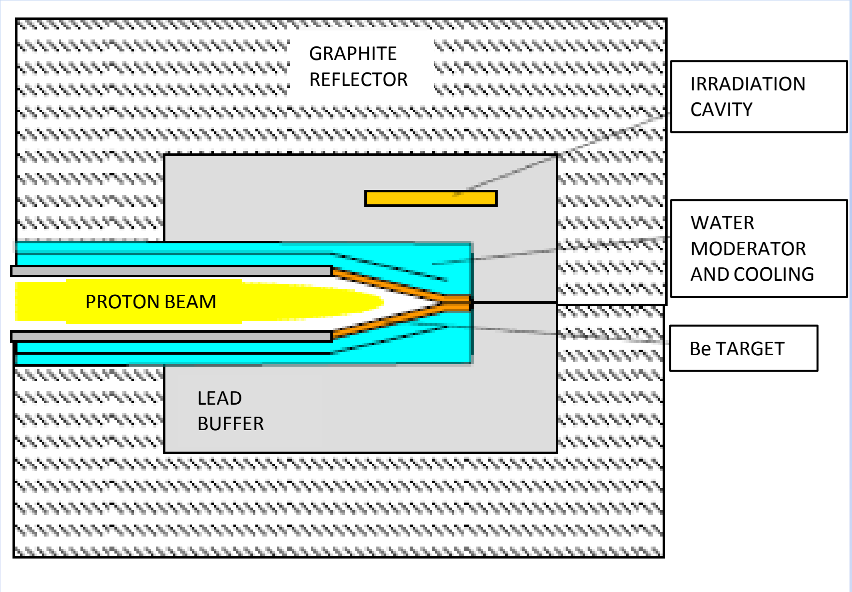
Courtesy S. Buono, *AAA*

Accelerator-driven neutron activator

- Fast neutron flux generated in a Be target by protons
- Neutrons are down-scattered with low parasitic capture in a lead/graphite assembly surrounding the Be target (the C reflector ensuring a fast thermalisation)
- Material to be activated is located in irradiation channels where the neutron flux is optimized for the capture reaction of interest
- Activation yields measured for Au, Al, Mo, Ho and Re foils

Test at the JRC Ispra

Scanditronix MC40 cyclotron



K. Abbas et al, Design and test of an accelerator driven neutron activator at the JRC cyclotron of the European Commission, Proc. Cyclotrons and Their Applications, 2007, 18th International Conference, p. 228

Industrial production of ^{99}Mo by ARC

- A high-power proton accelerator (1 mA at 1 GeV = 1 MW beam power):
  - Linac (ESS in Lund)
  - Cyclotron (PSI)
  - FFAG (KEK)

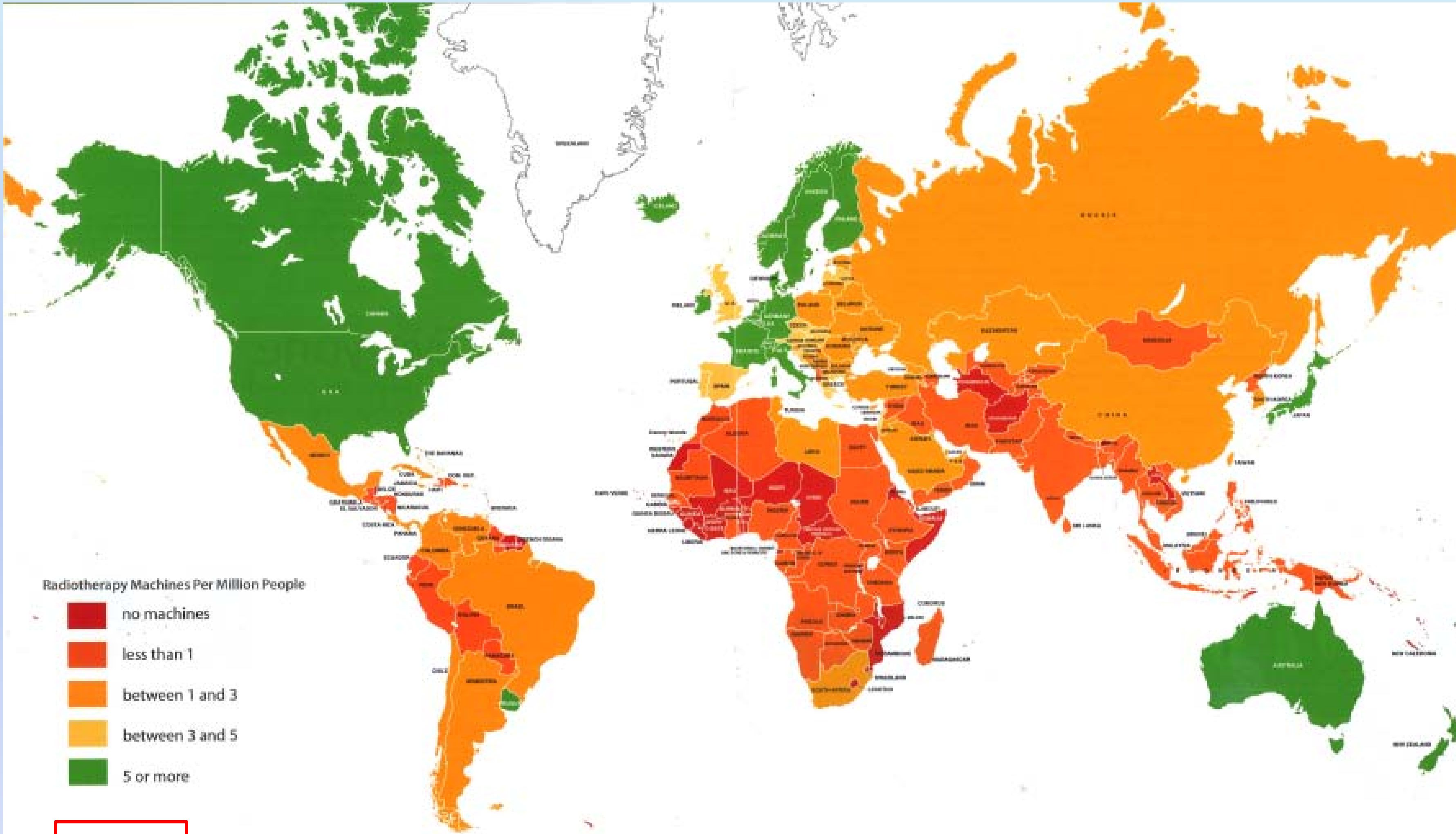
12-sector 150 MeV FFAG at KEK

capable of providing a flux of neutrons equivalent to a research reactor but with the “quality” suited to enhance the ARC effect and therefore the production of ^{99}Mo from Natural Enriched ^{98}Mo

- One accelerator could cover 100% of the current world demand of ^{99}Mo (not currently possible with reactors)

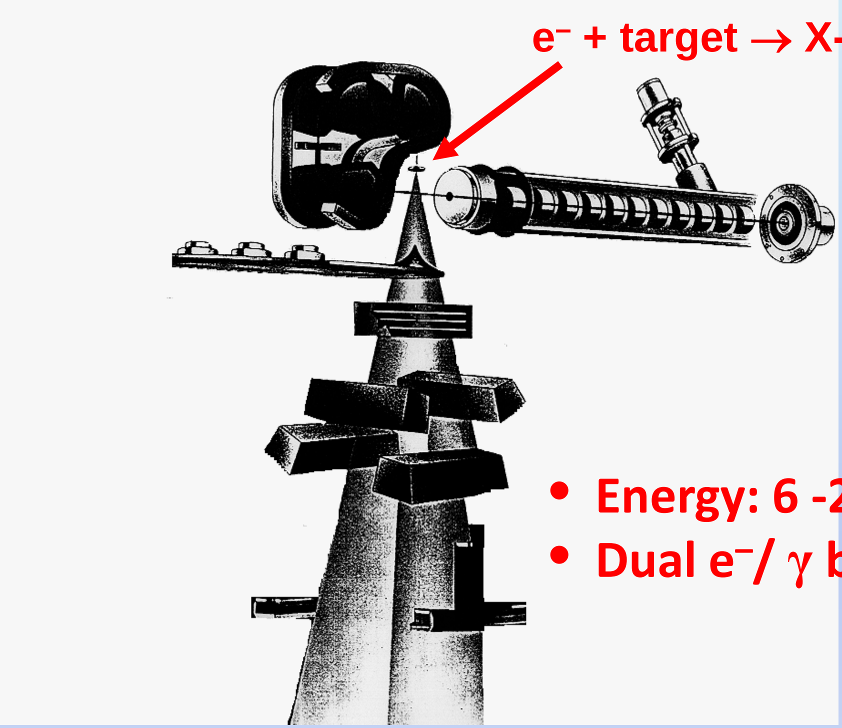
“Conventional” radiation therapy

Availability of radiation therapy worldwide

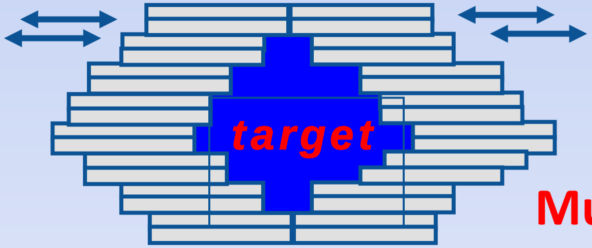


Number of radiation therapy machines per million people

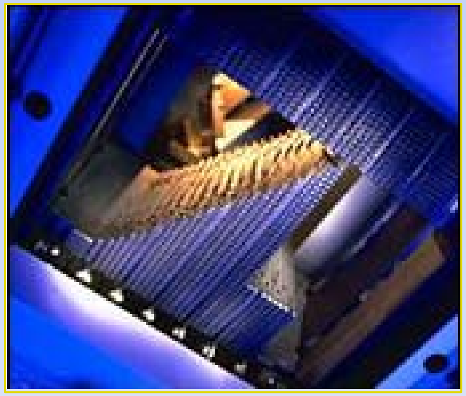
Medical electron linacs



- **Energy: 6 -25 MeV**
- **Dual e⁻/ γ beams**



Multi-leaf collimator

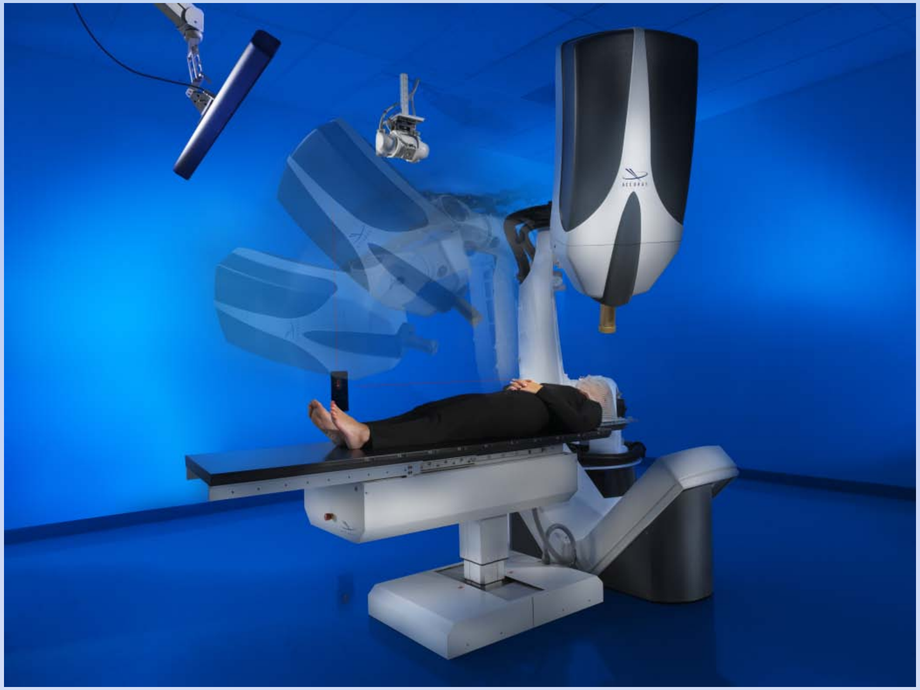


Intra-Operative Radiation Therapy (IORT)

- Small electron linac
- Energy 6 – 12 MeV
- Treatment with electrons only
- Single irradiation
- Three models of linac produced by three manufacturers

CyberKnife Robotic Surgery System

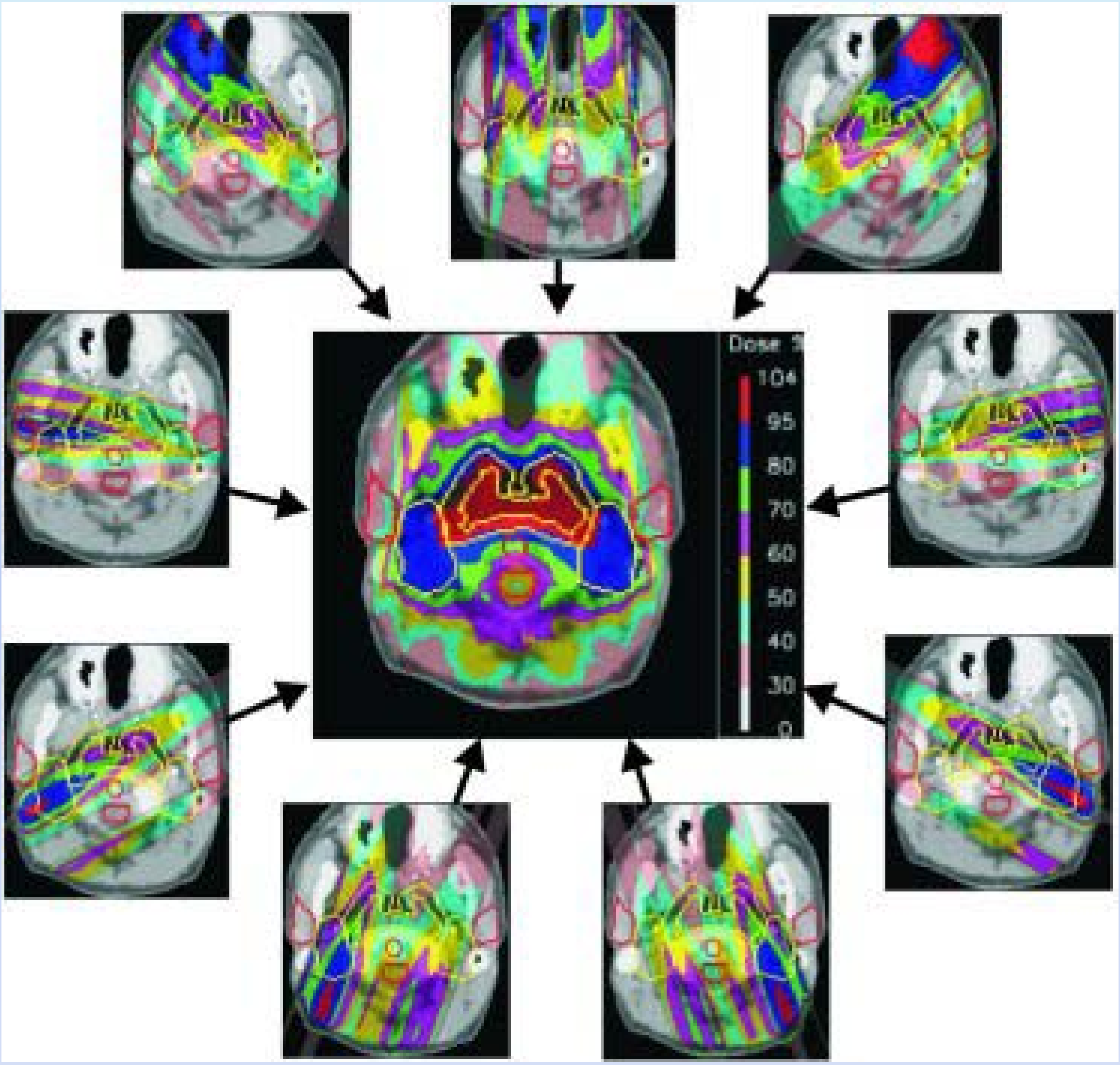
6 MV Linac mounted on a robotic arm



- No flattening filter
- Uses circular cones of diameter 0.5 to 6 cm
- Non-Isocentric
- Average dose delivered per session is 12.5 Gy
- 6 sessions/day
- Dose rate @ 80 cm = 400 cGy/min

http://www.accuray.com/Products/Cyberknife/index.aspx

Intensity Modulated Radiation Therapy (IMRT)

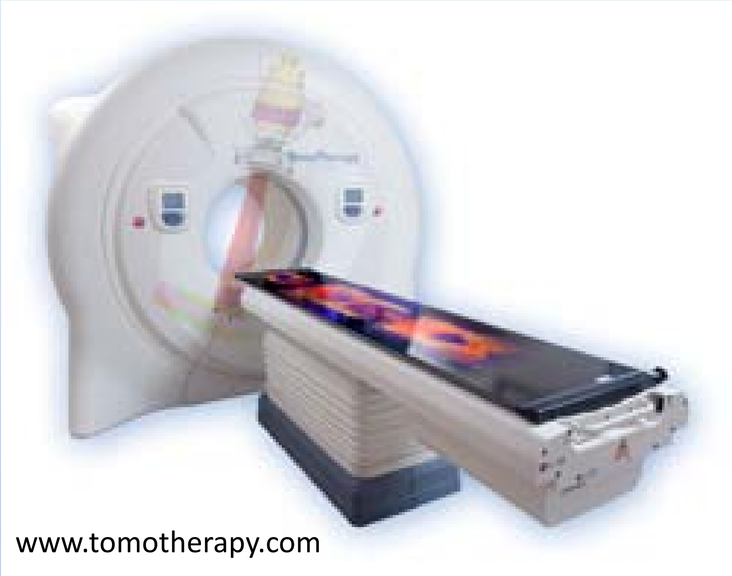


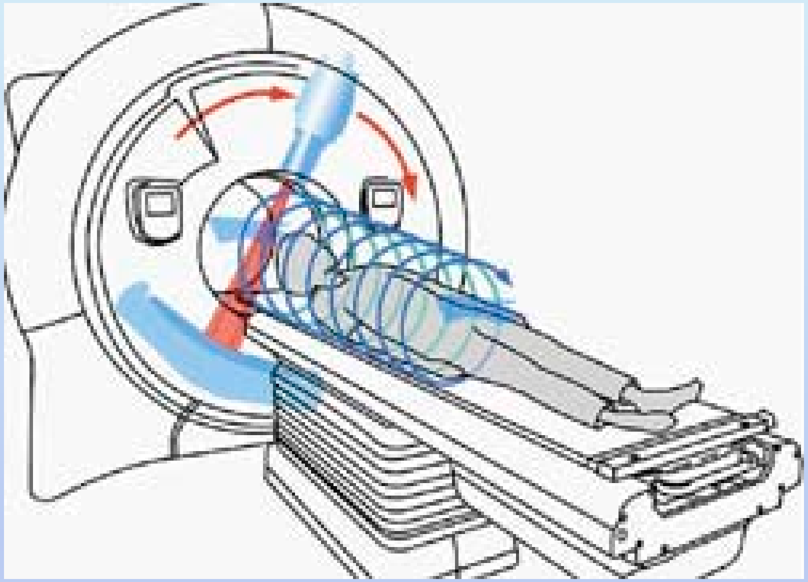
An example of intensity modulated treatment planning with photons. Through the addition of 9 fields it is possible to construct a highly conformal dose distribution with good dose sparing in the region of the brain stem (courtesy of T. Lomax, PSI).

E. Pedroni, Europhysics News (2000) Vol. 31 No. 6

Yet X-rays have a comparatively poor energy deposition as compared to protons and carbon ions

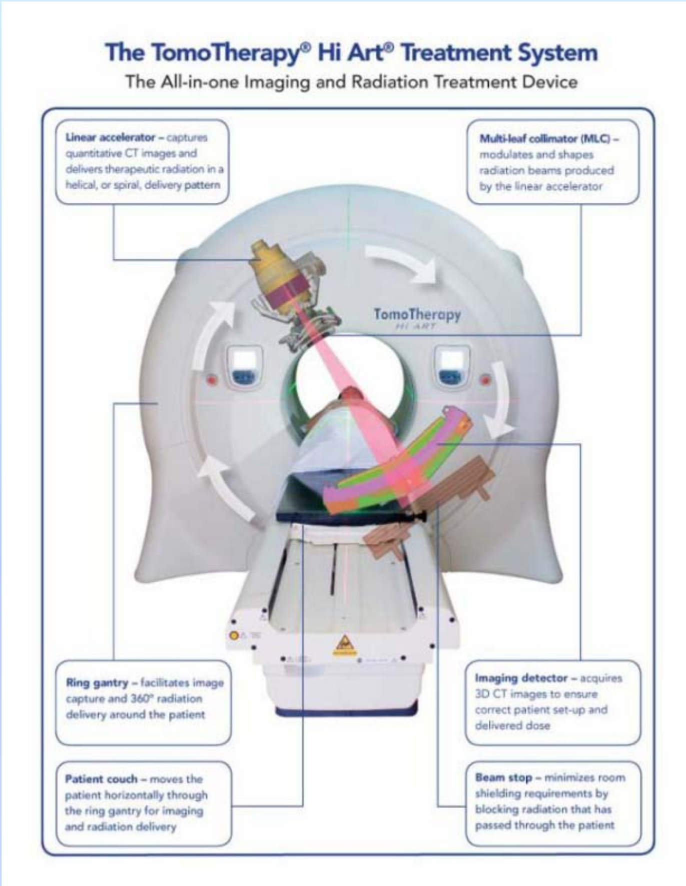
Helical tomotherapy



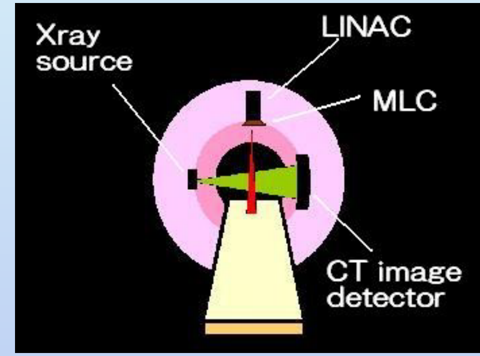


- Integrated CT guidance
  - Integrated CT scanner allowing efficient 3D CT imaging for ensuring the accuracy of treatment
- A binary multi-leaf collimator (MLC) for beam shaping and modulation
- A ring gantry design enabling TomoHelical delivery
  - As the ring gantry rotates in simultaneous motion to the couch, **helical fan-beam IMRT** is continuously delivered from all angles around the patient
  - Very large volumes can be treated in a single set-up

Helical tomotherapy



www.tomotherapy.com

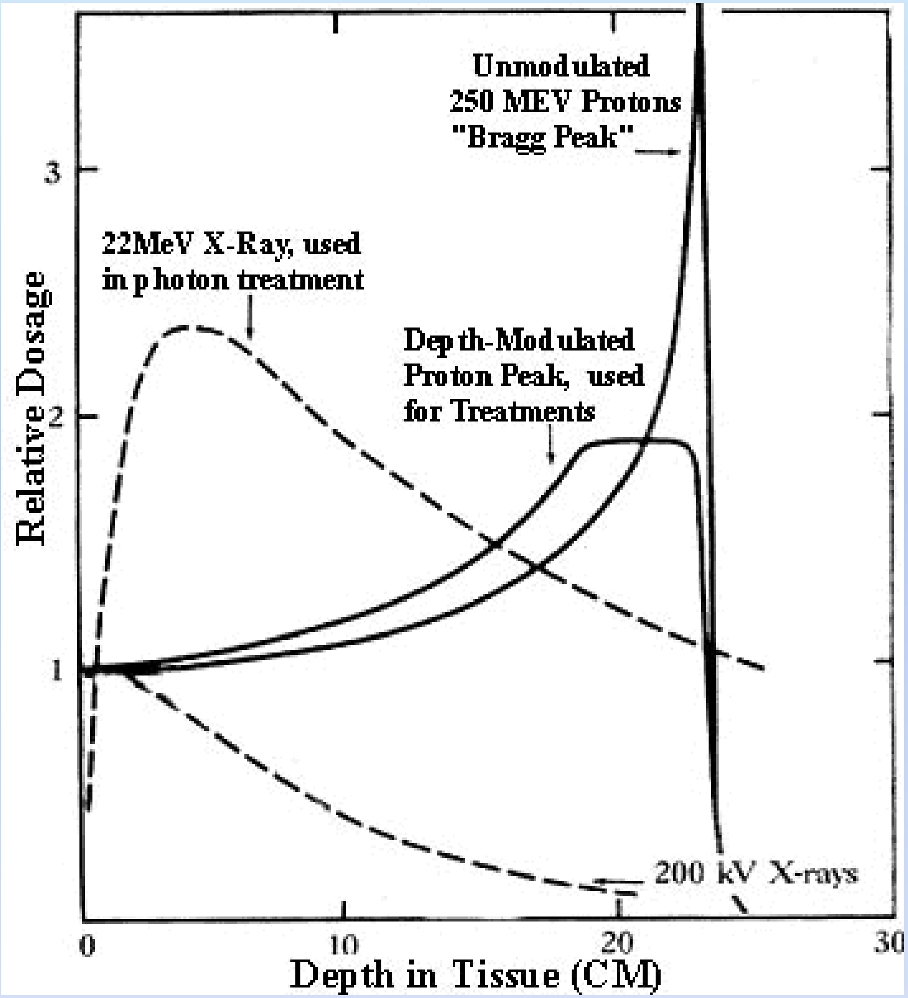


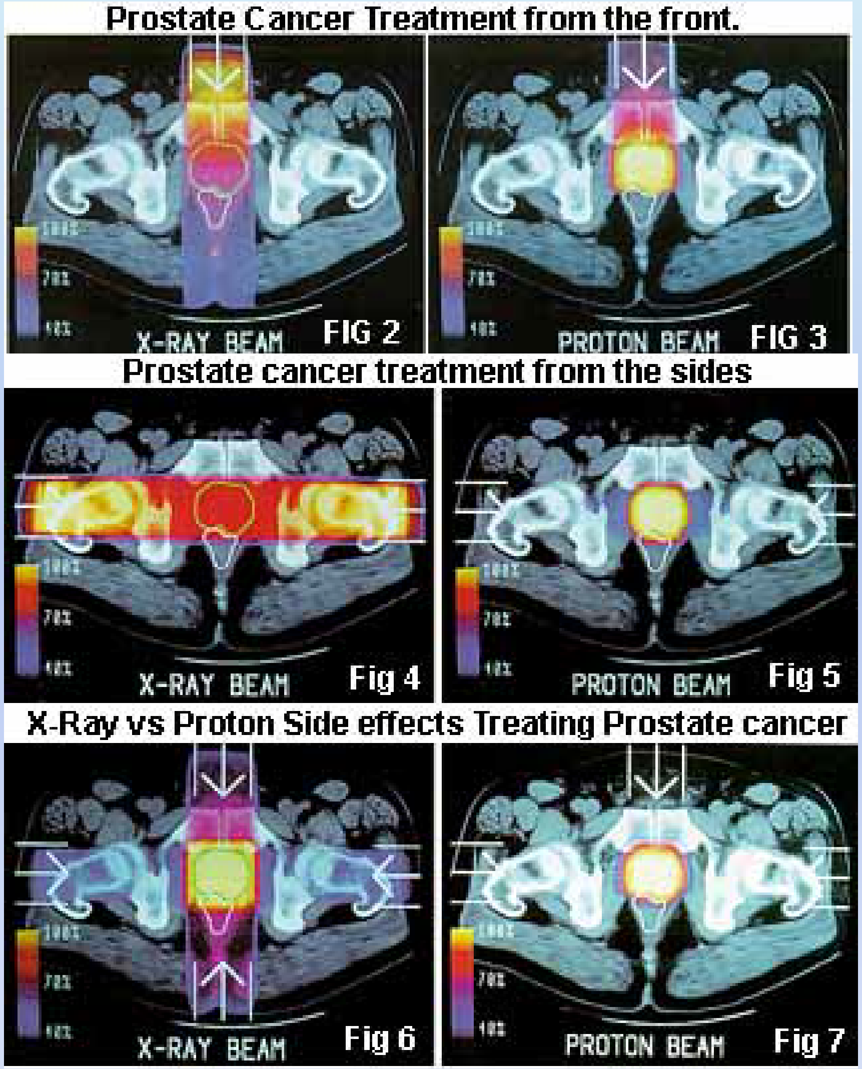
- It combines image-guided and intensity-modulated radiation therapy (IG/IMRT)
- It optimizes the weight of the tens of thousands of beamlets used in a typical *TomoTherapy* radiation treatment fraction
  - Each beamlet weight corresponds to the “opening time” of a single leaf in the MLC at a given stage of delivery

- Adaptive Radiation Therapy (ART)
  - Patients lose weight
  - Targets and organs shift and deform relative to the plan

Hadron-therapy

Proton radiation therapy

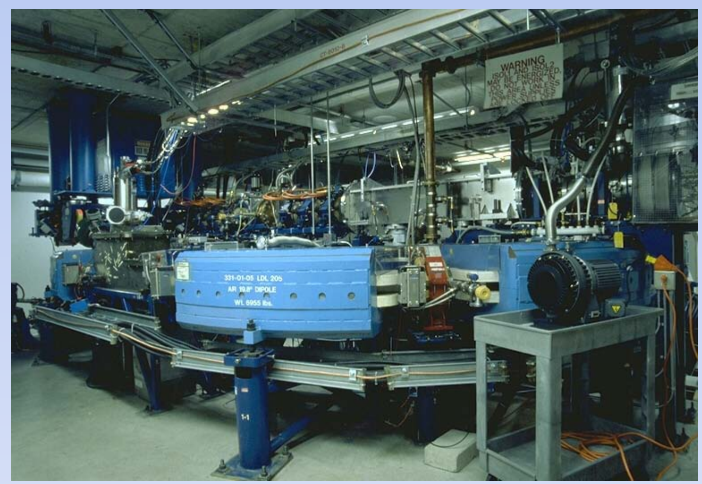




Cyclotrons and synchrotrons for PT

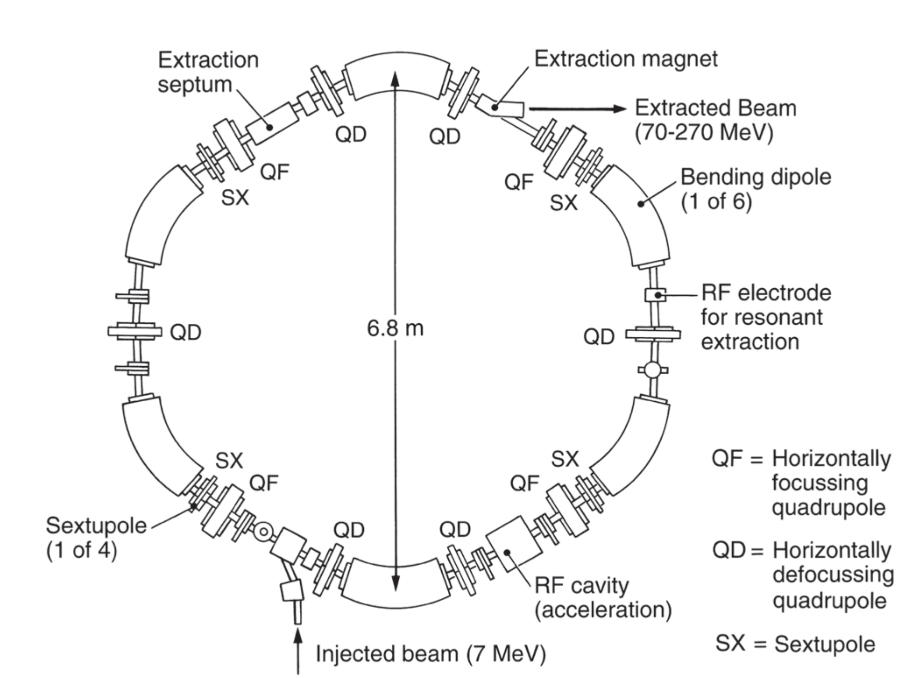
Accel-Varian

Loma Linda
(built by FNAL)

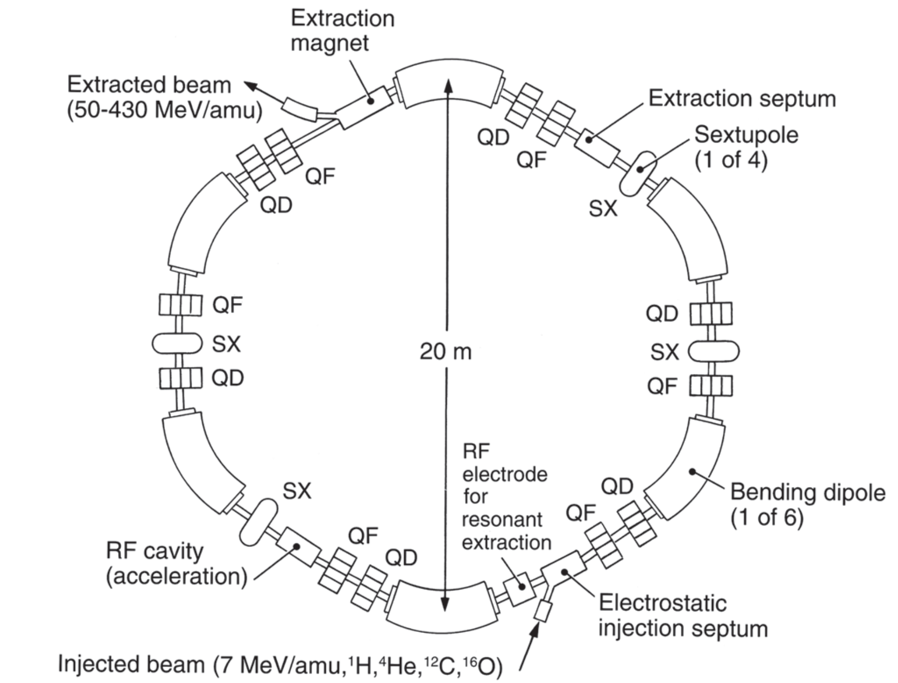


Proton versus carbon-ion synchrotrons

Hitachi proton synchrotron

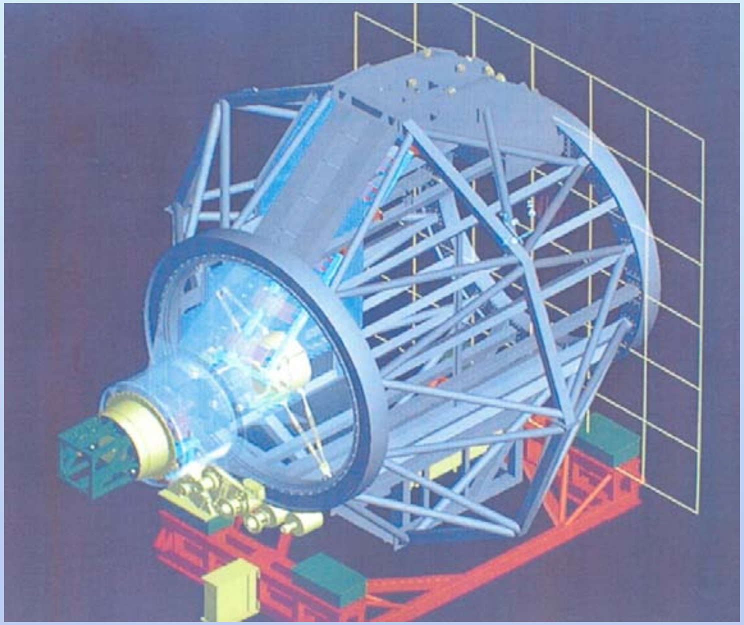


Siemens ion synchrotron



G. Coutrakon, Accelerators for Heavy-charged-particle Radiation Therapy,
Technology in Cancer Research & Treatment, Volume 6, Number 4 Supplement, August 2007

A PT facility is not just the accelerator…



ISOCENTRIC GANTRY

A gantry is a massive structure that allows directing the beam to the tumour from any direction. It carries

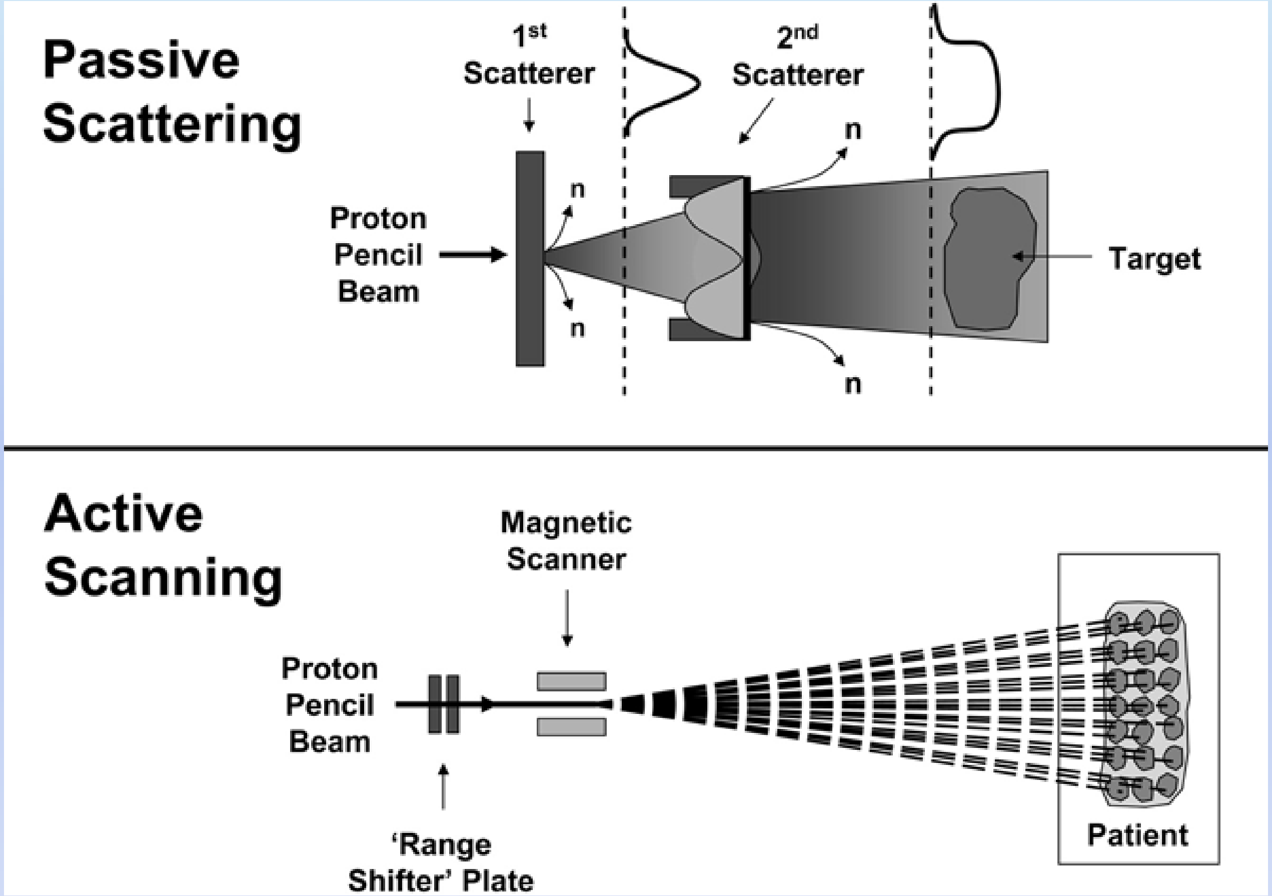
- the final section of the beam line
- the beam spreading 'nozzle'
- the proton 'snout' which carries the aperture and range compensator

What it looks like to the patient: gantry room at the Midwest Proton Radiotherapy Institute (MPRI) (modified IBA gantry)

Adapted from B. Gottschalk

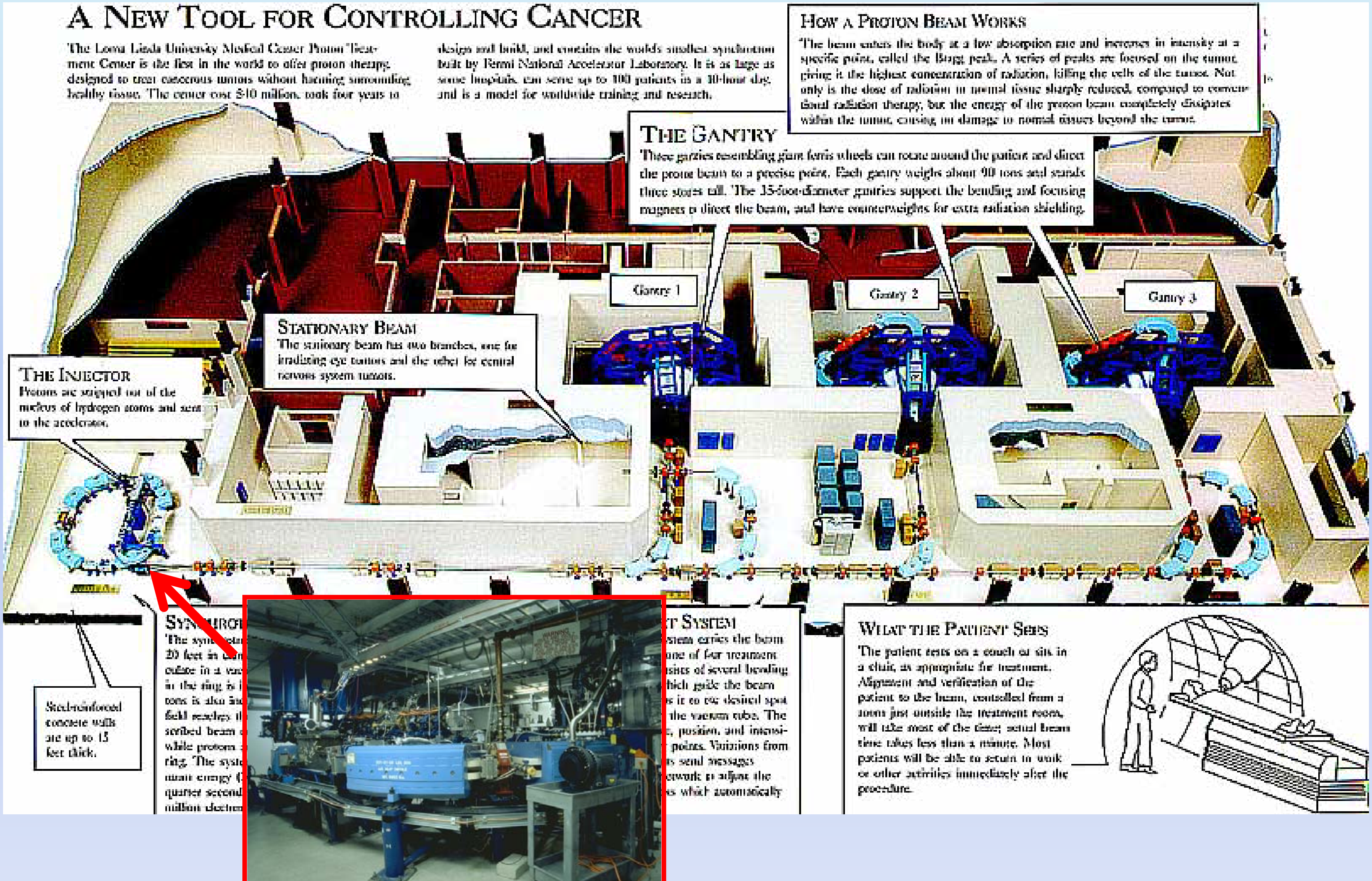
A PT facility is not just the accelerator…

Passive (double scattering) versus active (scanning) beam delivery



From E.J. Hall, Int. J. Radiat. Oncol. Biol. Phys. **65**, 1-7 (2006)

Loma Linda University Medical Center (LLUMC)



Hadron-therapy in Europe

O in operation
in construction
Δ planned

Yellow = p only
Orange = p and C

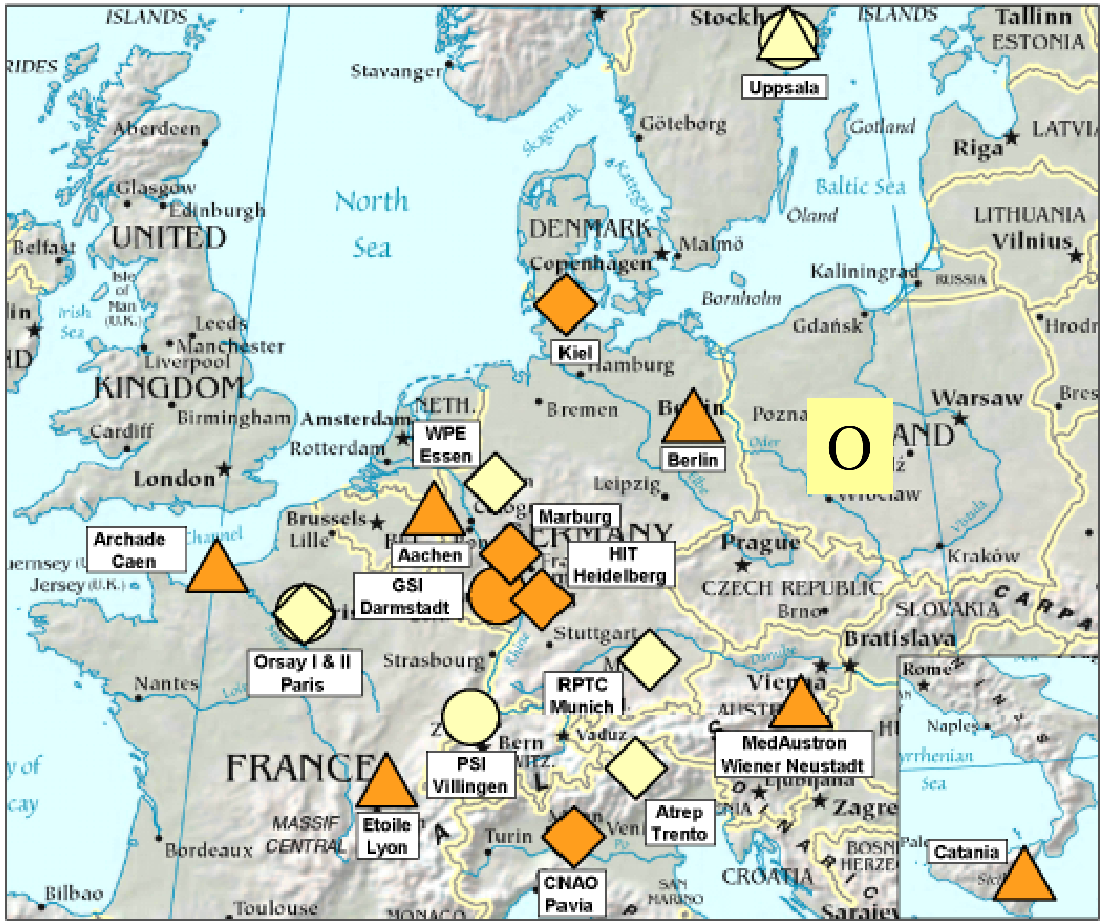
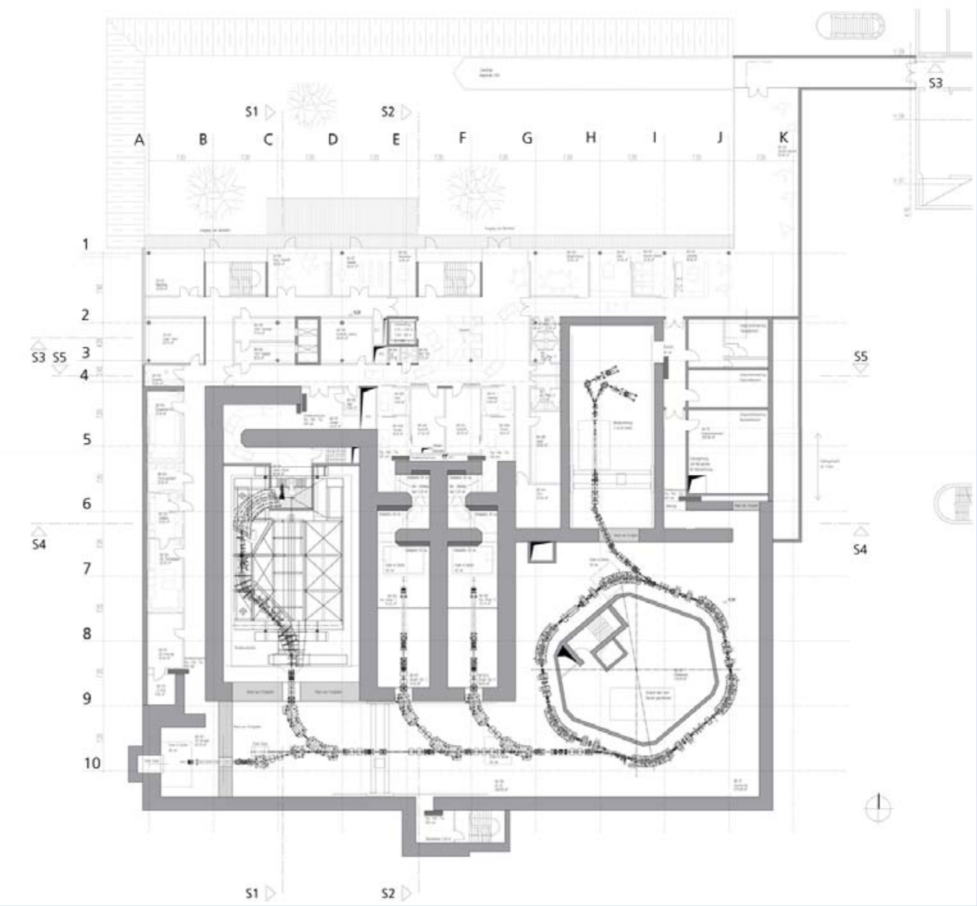
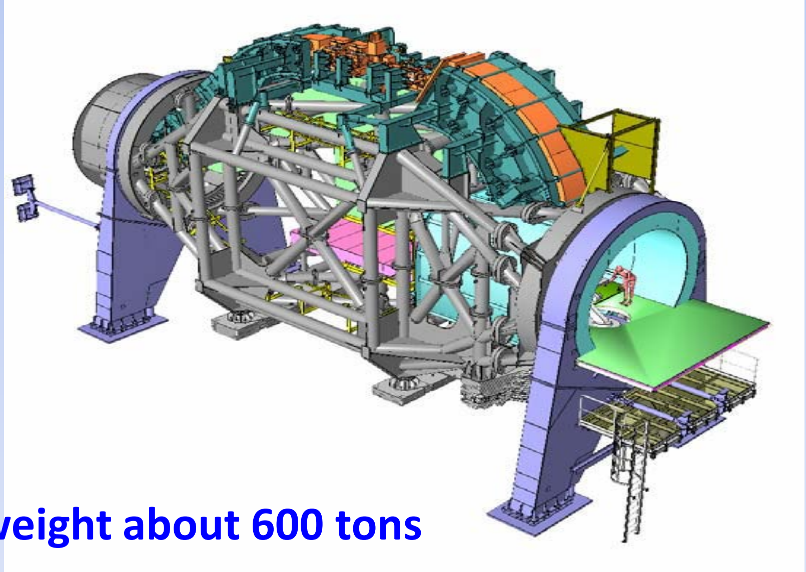


FIGURE 1. Map of Europe showing the present status of the ion beam therapy. The status of different projects is given by the symbols: in operation ◯; under construction ◇; planned △. The type of the facilities is indicated by the colors: yellow – proton only; orange – Carbon and protons.

G. Kraft, Proc. of CAARI 2008, AIP, p. 429

Heavy Ion Therapy Unit at the University of Heidelberg clinics

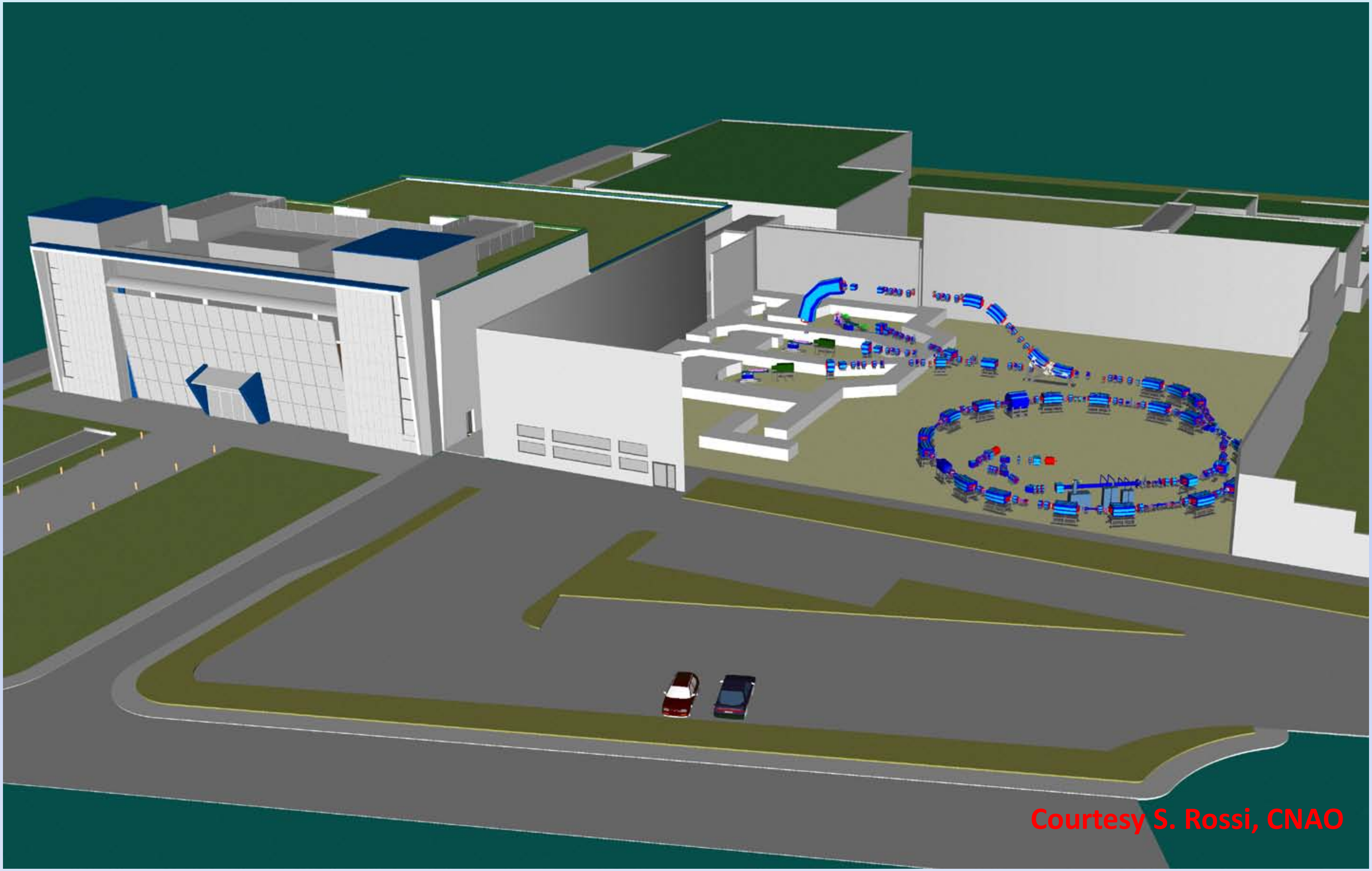




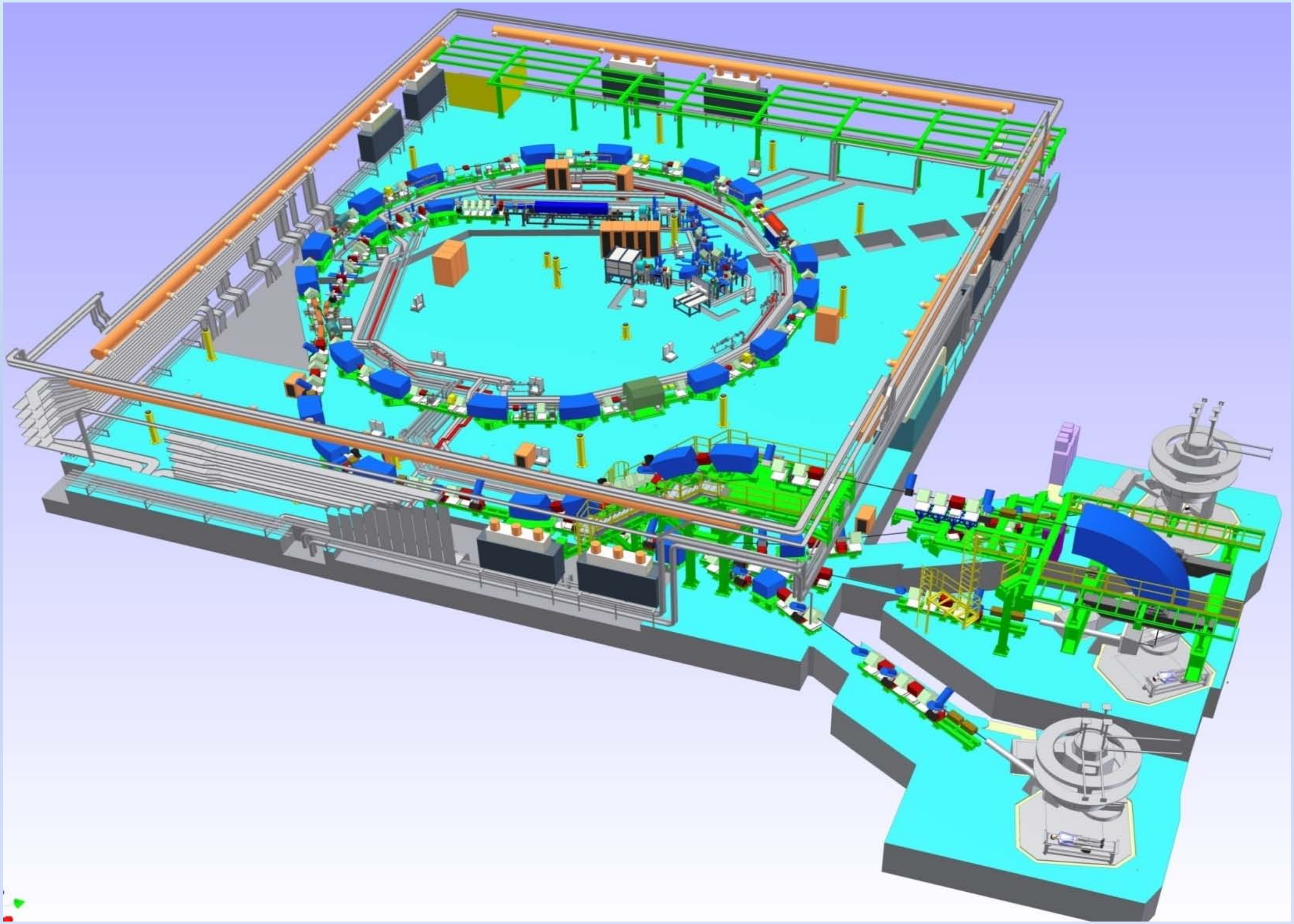
Courtesy HIT

The HIT heavy ion gantry, weight about 600 tons

National Centre for Oncological Hadrontherapy (CNAO) in Pavia

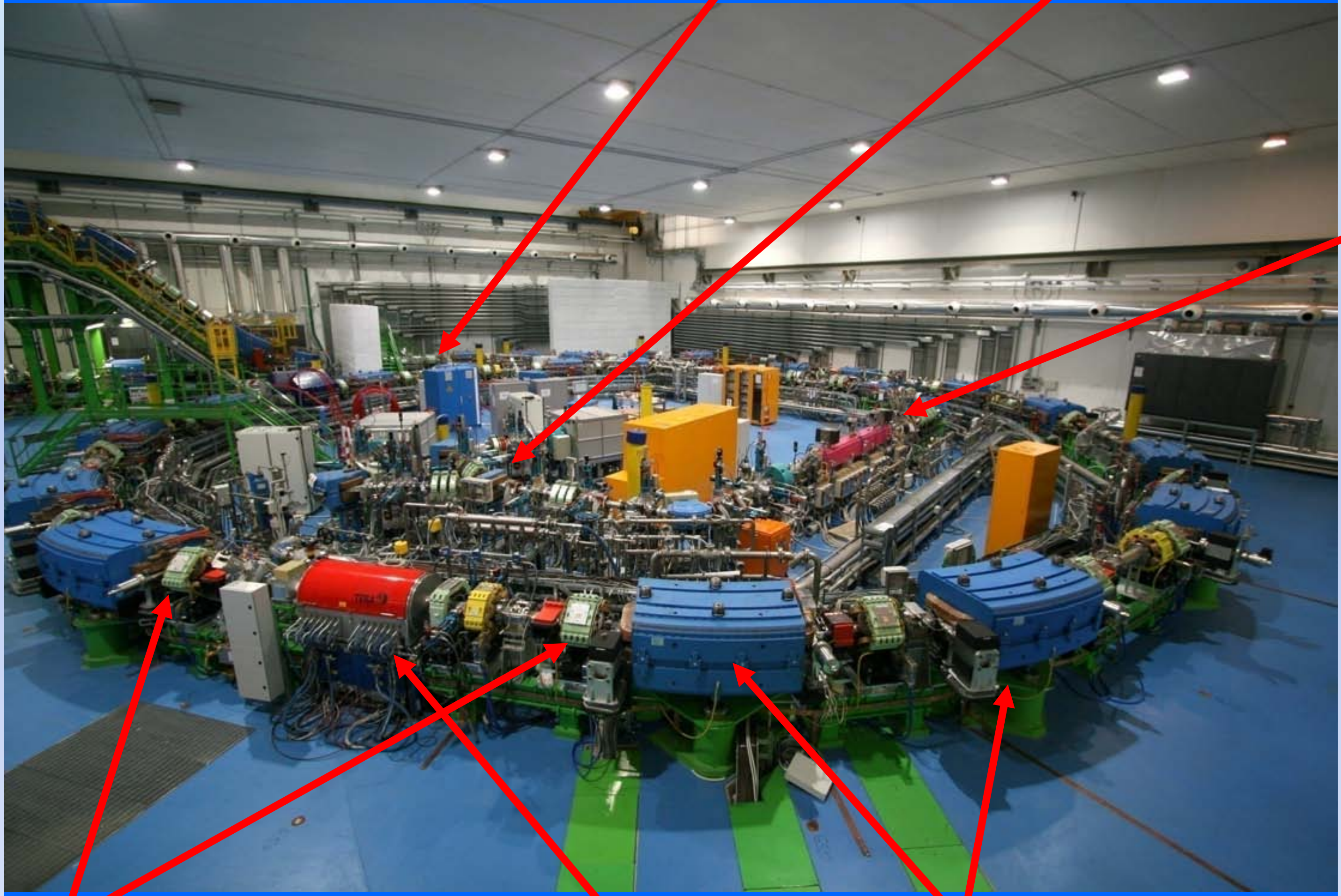


CNAO in Pavia

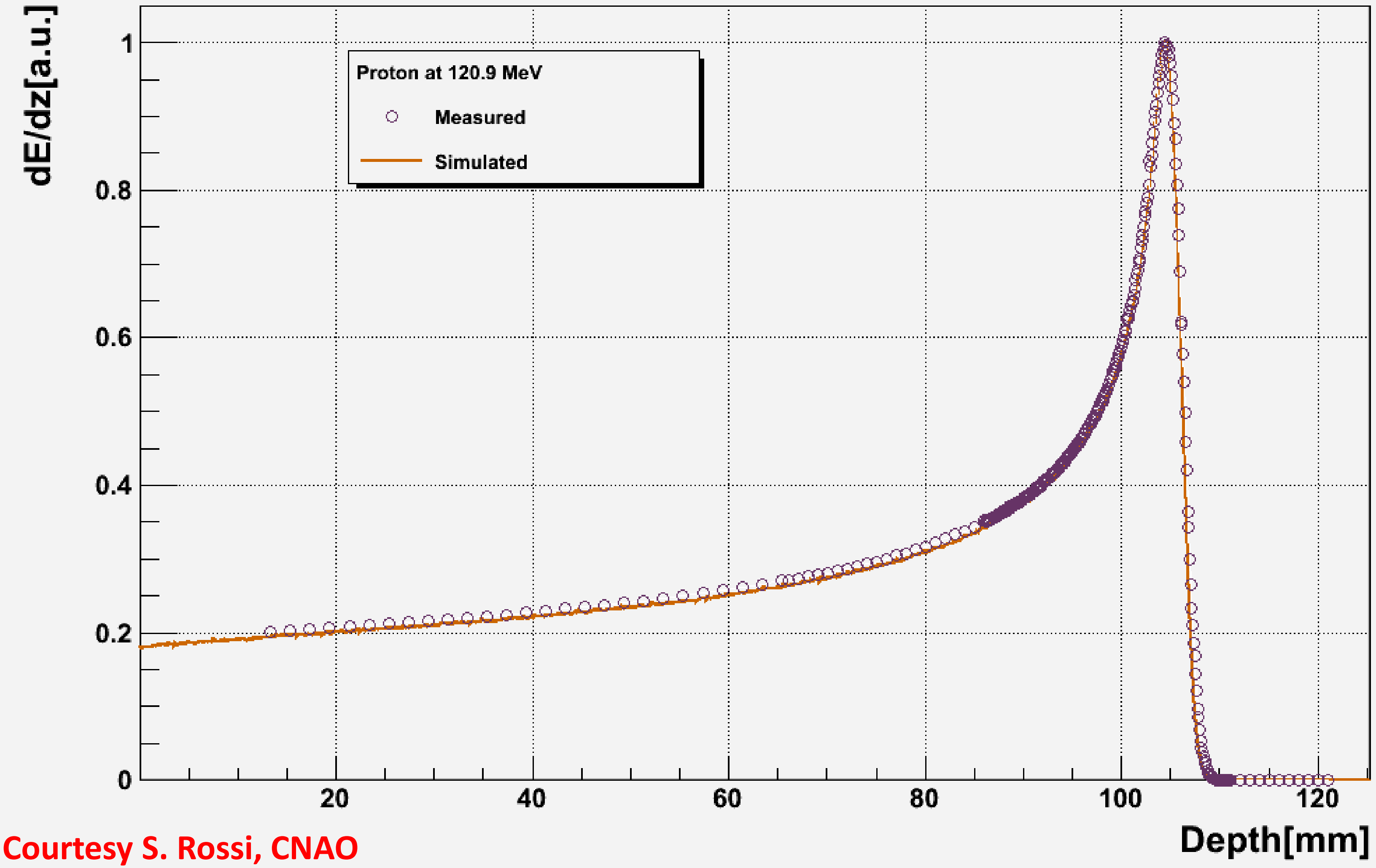


The CNAO synchrotron

Courtesy S. Rossi, CNAO



Commissioning of the CNAO clinical beam

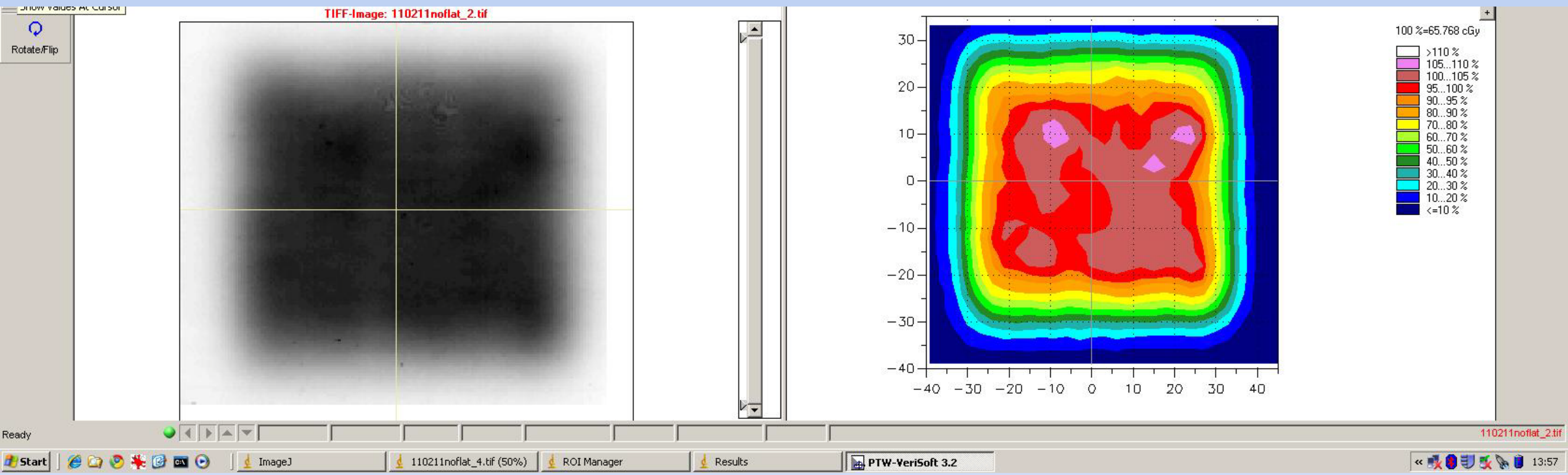


Courtesy S. Rossi, CNAO

Commissioning of the CNAO clinical beam

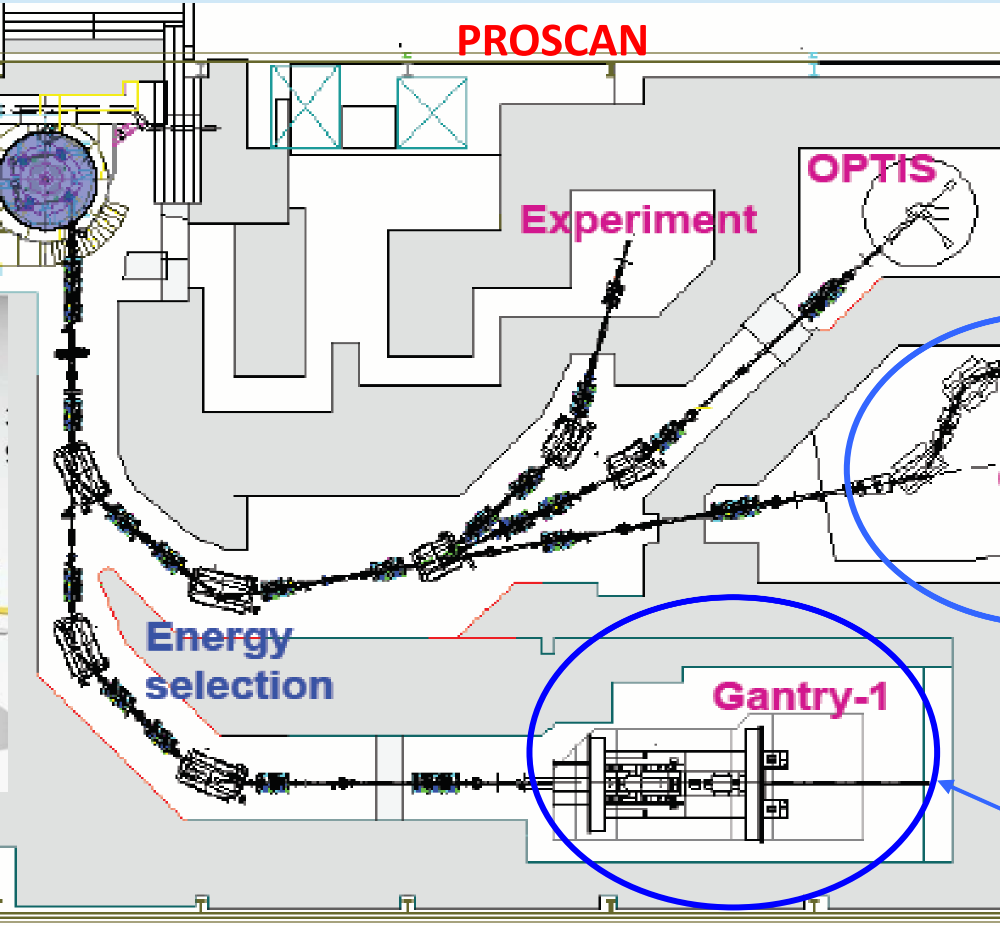
Beam uniformity measurements

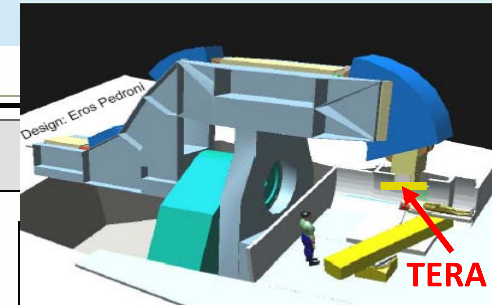
Dimensions (cm x cm)	N. scan	N. spot	cnts/ spot	N. spill	Time	Omog. (%)	Dose film (Gy)	FWHM at isoc. (cm)	Step scans. (mm)
~ 6 x 5	1	1600	1000	6	36 s	2	0,66	1,2 circa	1,5

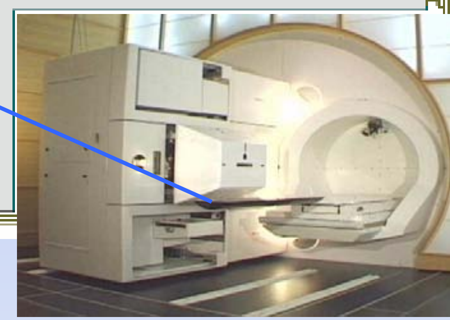


Courtesy S. Rossi, CNAO

PROSCAN at PSI, Switzerland



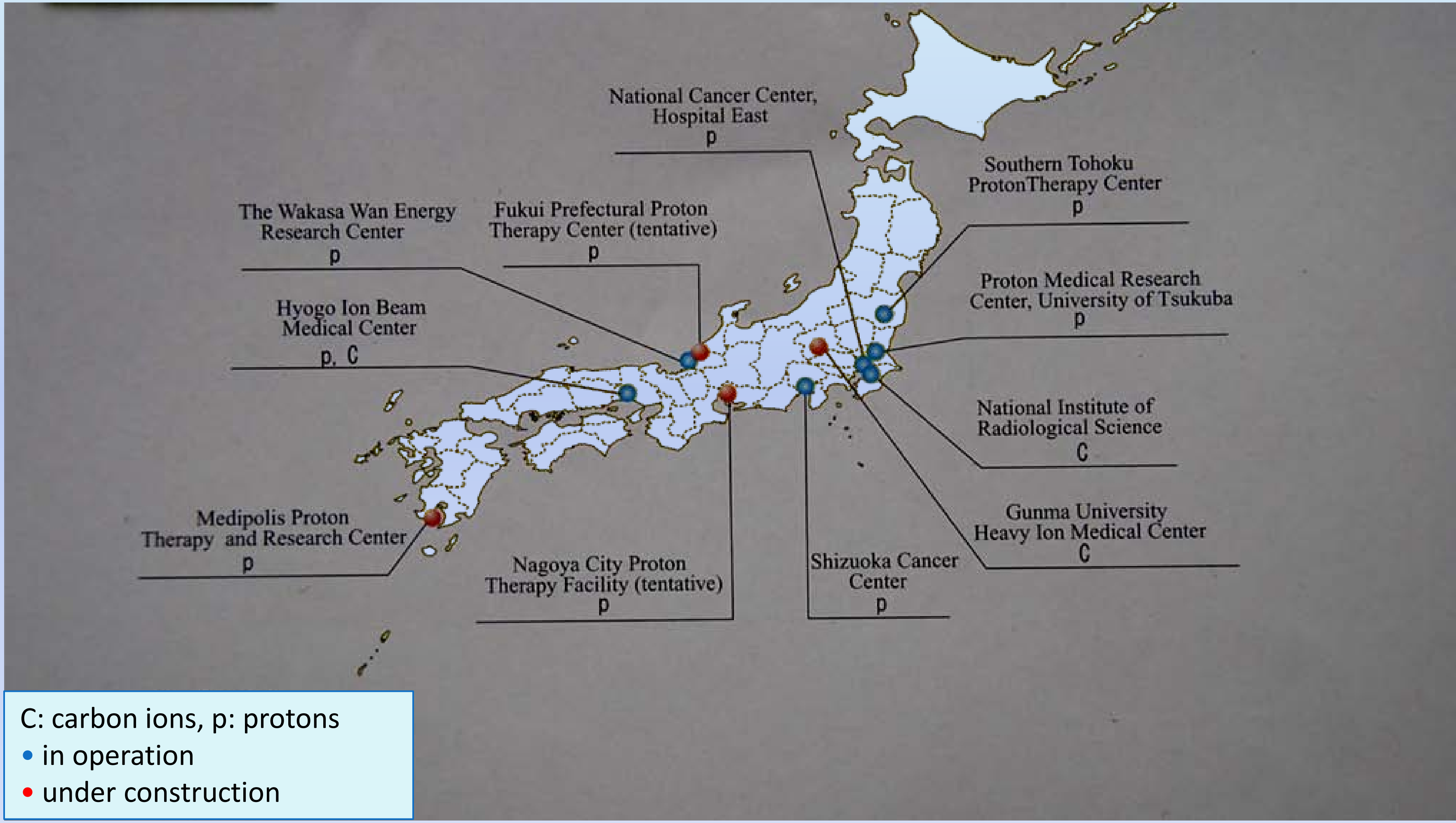




Courtesy PSI and U. Amaldi , *TERA*

J.M. Schippers et al., NIM BB 261 (2007) 773–776

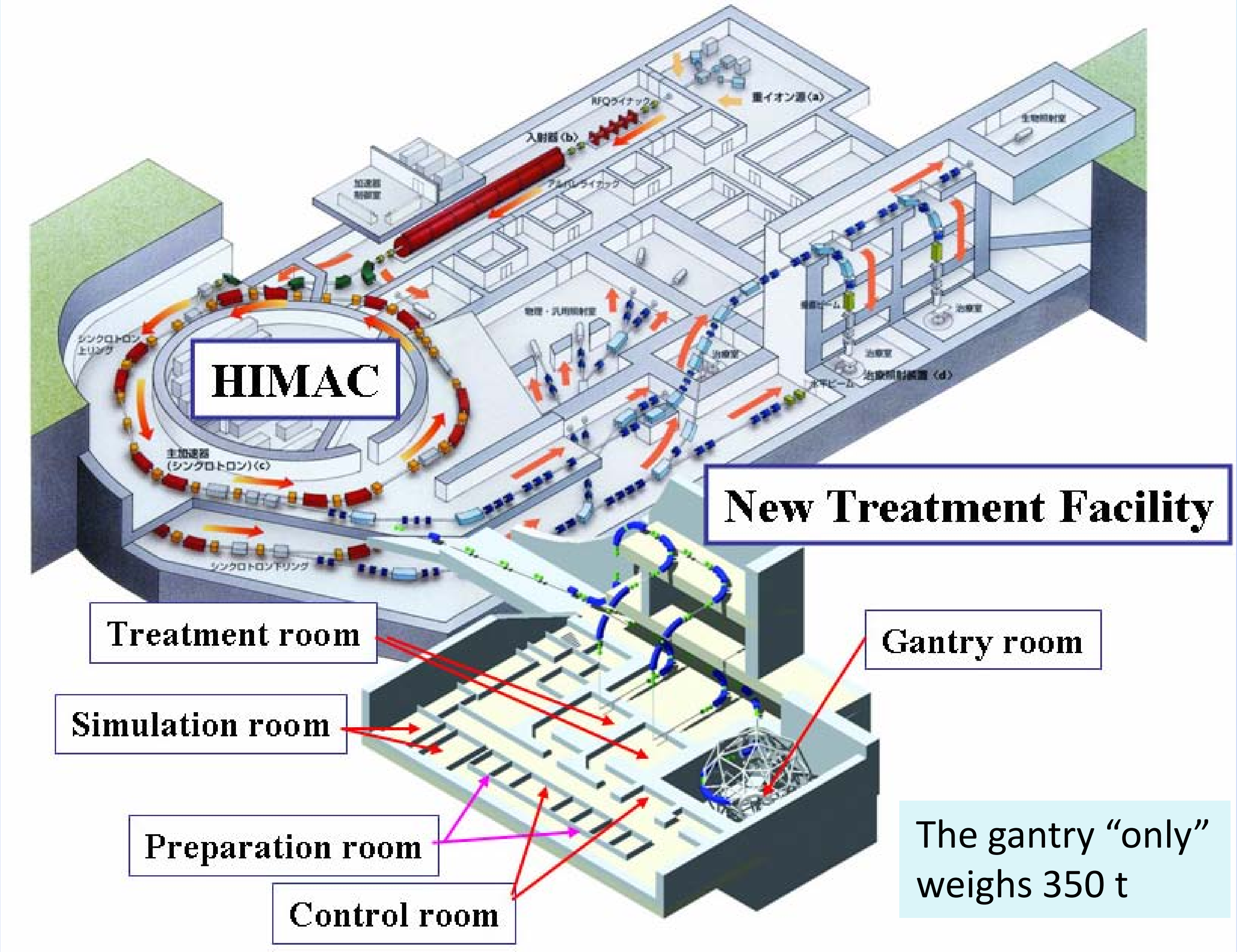
Hadron-therapy in Japan



C: carbon ions, p: protons
- in operation
- under construction

Courtesy NIRS

HIMAC in Chiba



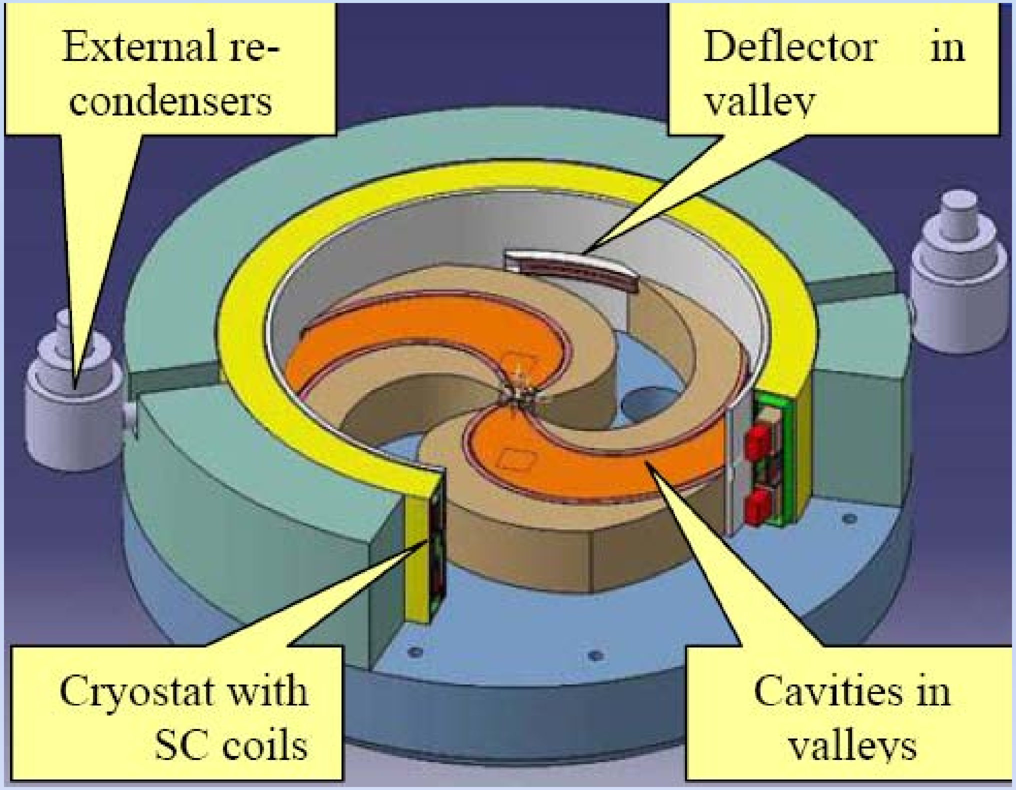
The gantry "only" weighs 350 t

K. Noda et al., Recent progress on HIMAC for carbon therapy, Proc. of PAC09

New concepts

IBA 400 MeV/u C-ion cyclotron

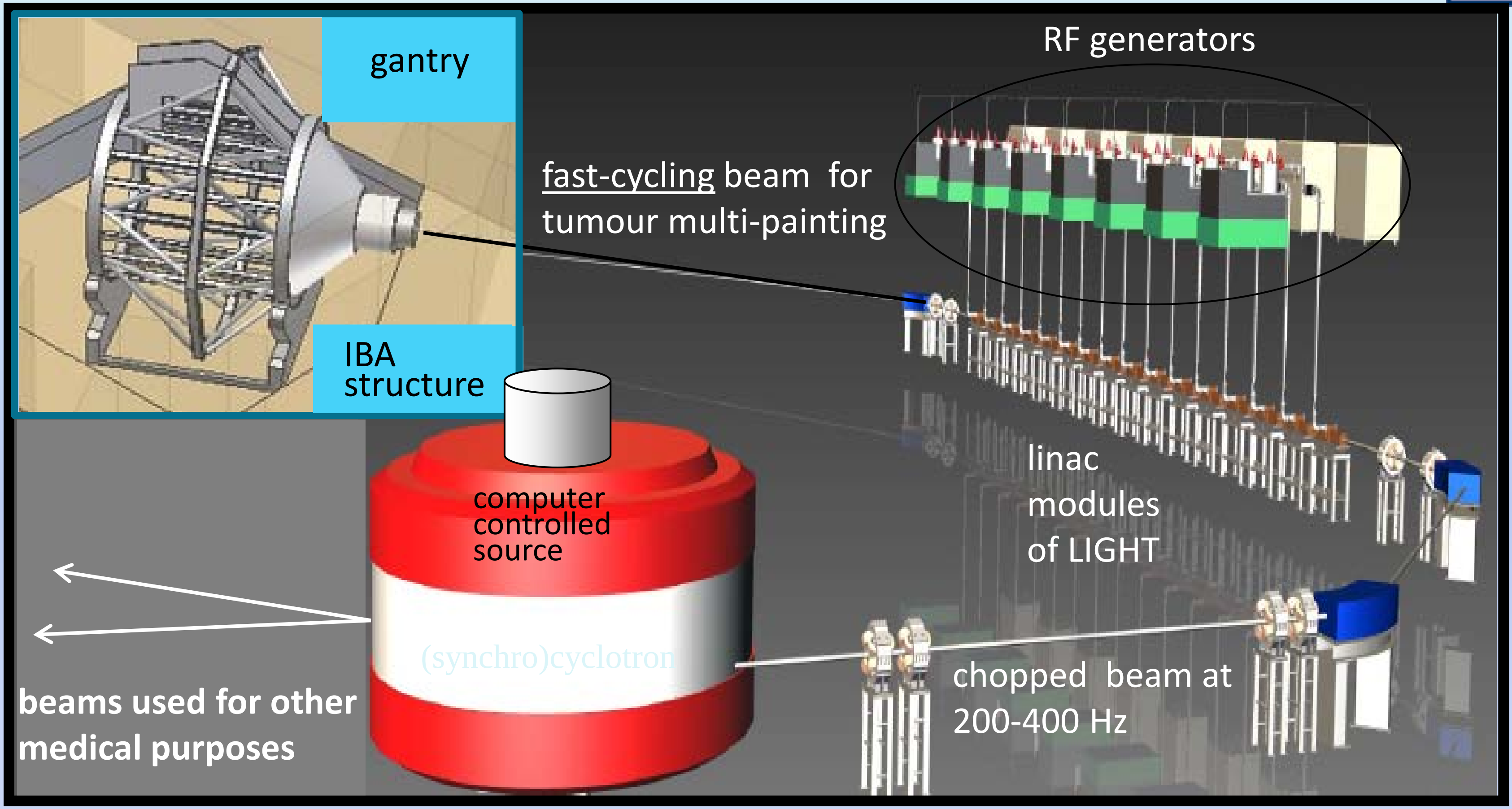
"Archade" (at Ganil in Caen, France) is based on the new IBA 400 MeV/u superconducting cyclotron



- **Maximum energy: 400 MeV/u, adjustable externally by ESS**
- **Superconducting magnet. Hill field 4.5 T**
- **Cooling by helium loop, with 4 external recondensers**

Courtesy Y. Jongen, *IBA*

Cyclinac = Cyclotron+Linac for Image Guided HadronTherapy



The energy is adjusted in 2 ms in the full range by changing the power pulses sent to the 16-22 accelerating modules
The charge in the next spot is adjusted every 2 ms with the computer controlled source

Courtesy U. Amaldi, *TERA*

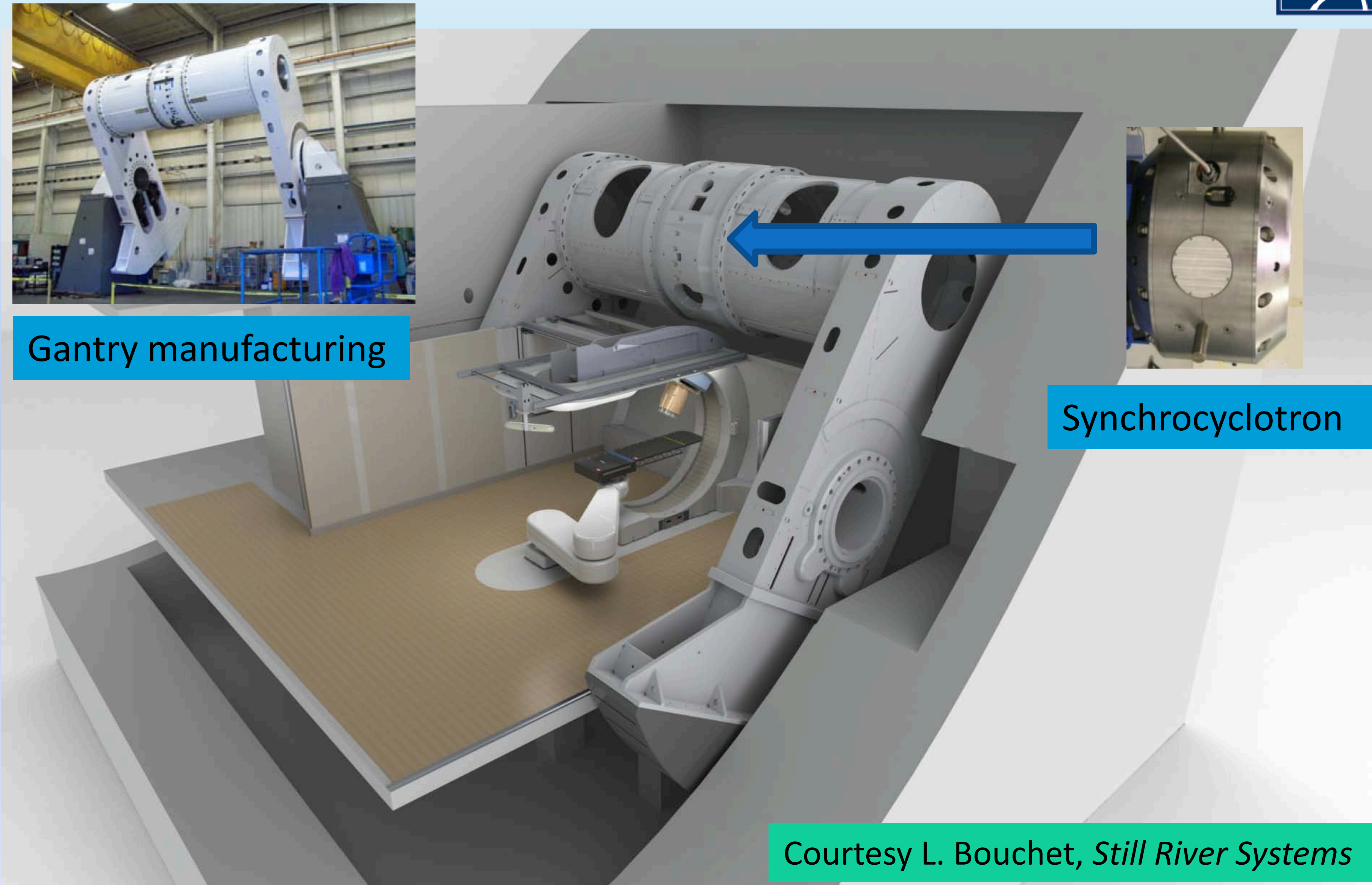
Still River Systems

Synchrocyclotron @ 10 Tesla
Proton energy: 250 MeV
Ion source tested up to 1,000 nA
Cooling is through cryo-compressors (NO liquid Helium)
Low maintenance requirements – quarterly only
Time structure: similar to linear accelerator <u>with gating and scanning capabilities</u>

Weight ≈ 20 tons

Courtesy L. Bouchet, *Still River Systems*

Still River Systems (founded 2004)



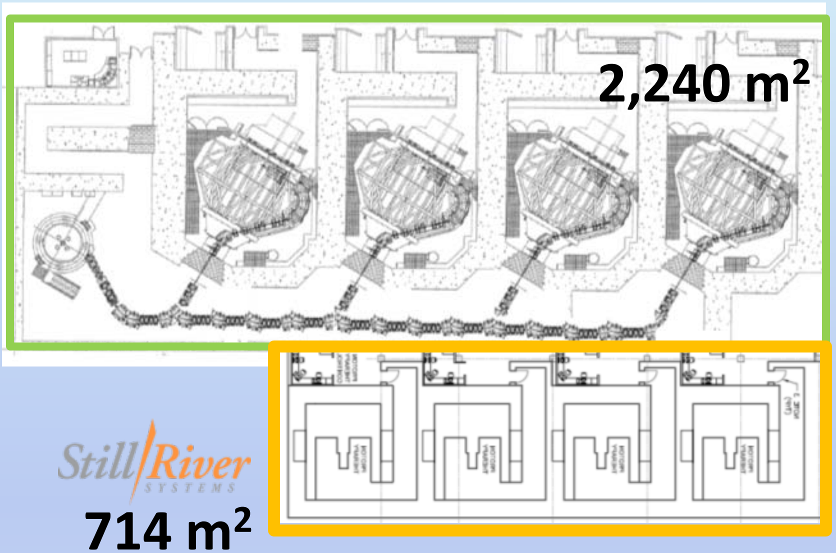
Gantry manufacturing

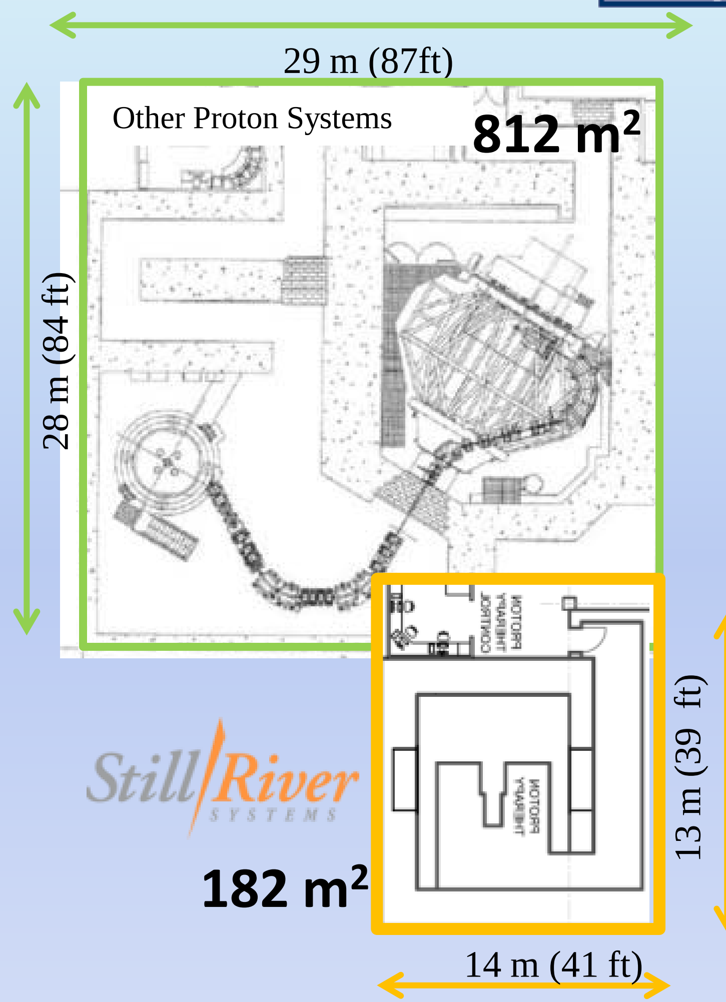
Synchrocyclotron

Courtesy L. Bouchet, *Still River Systems*

Still River Systems (founded 2004)

Multi-room versus single-room facilities





Advantages of single-room facility:

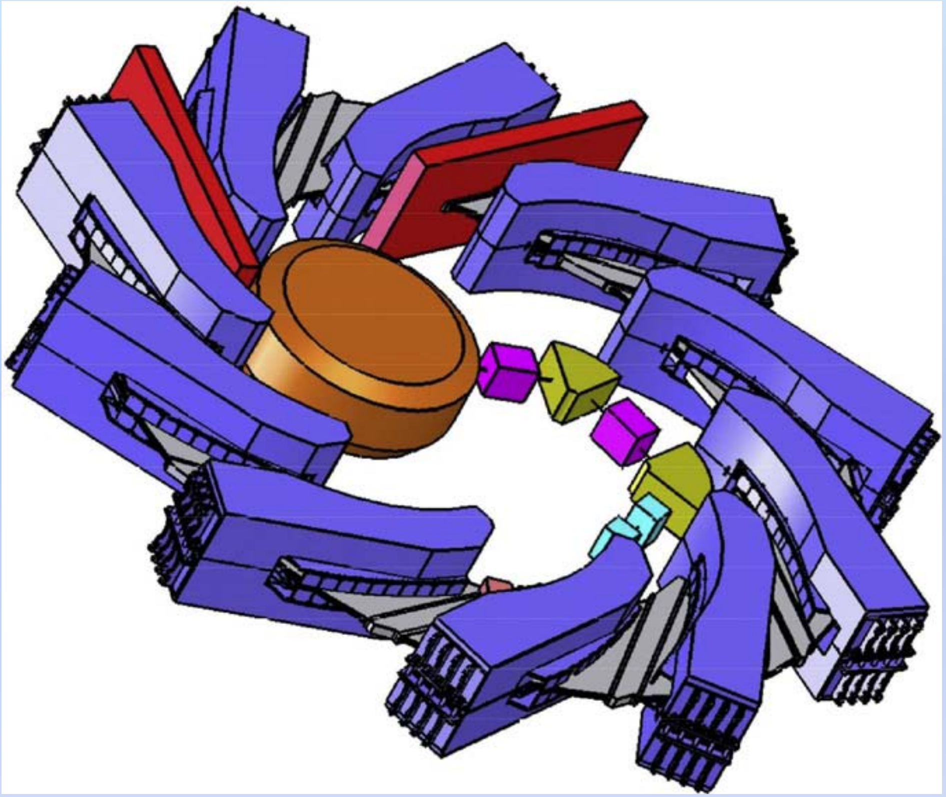
- ✓ **Modularity**
- ✓ **Reliability / back-up**
- ✓ **PT treatment available at more hospitals**
- ✓ **(Hopefully) cost**

Courtesy L. Bouchet, *Still River Systems*

FFAG accelerator for protons and light ions

RACCAM (Recherche en ACCélérateurs et Applications Médicales), Project leader F. Méot, CNRS

- FFAG: Fixed Field Alternating Gradient
  - ✓ a ring of magnets like a synchrotron
    BUT
  - ✓ fixed-field like in a cyclotron
- Non-pulsed power supplies, simple RF system, multi-particle, multi-port extraction
- Fast cycling
  - ✓ High dose rate
  - ✓ Slice-to-slice energy variation (100 ms)
  - ✓ 3D conformal therapy



Layout of the RACCAM FFAG assembly

S. Antoine et al, Nucl. Instr. Meth. A 602 (2009) 293-305

A look (far) into the future: laser accelerators

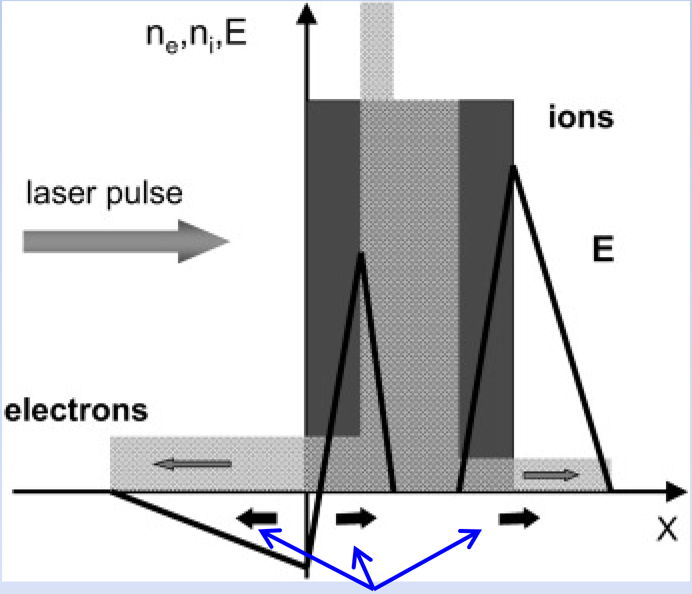
Large electric fields set up by laser-accelerated electrons at target interfaces

Very energetic beams of ions produced from laser irradiated thin metallic foils

- Electrons propagating forward into the target will set up fields in the interior of the target
- Very strong electric field (up to 30 % of the laser field →TV/m)
- Such fields can ionize atoms and rapidly accelerate ions swept from the target front surface in the *forward* direction

Charge and electric field distribution following high-intensity laser interaction with a solid foil.

M. Borghesi et al., Fast ion generation by high-intensity laser irradiation of solid targets and applications, Fusion science and technology 49, 412-439 (2006)

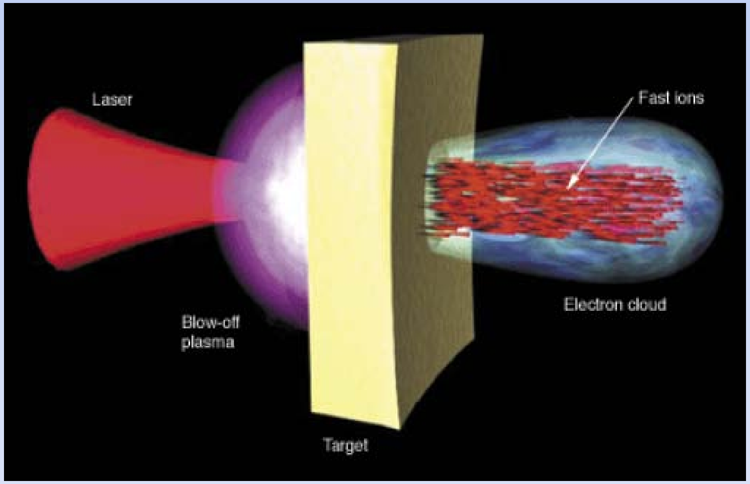


Fast ion motion

Laser accelerators for hadron therapy

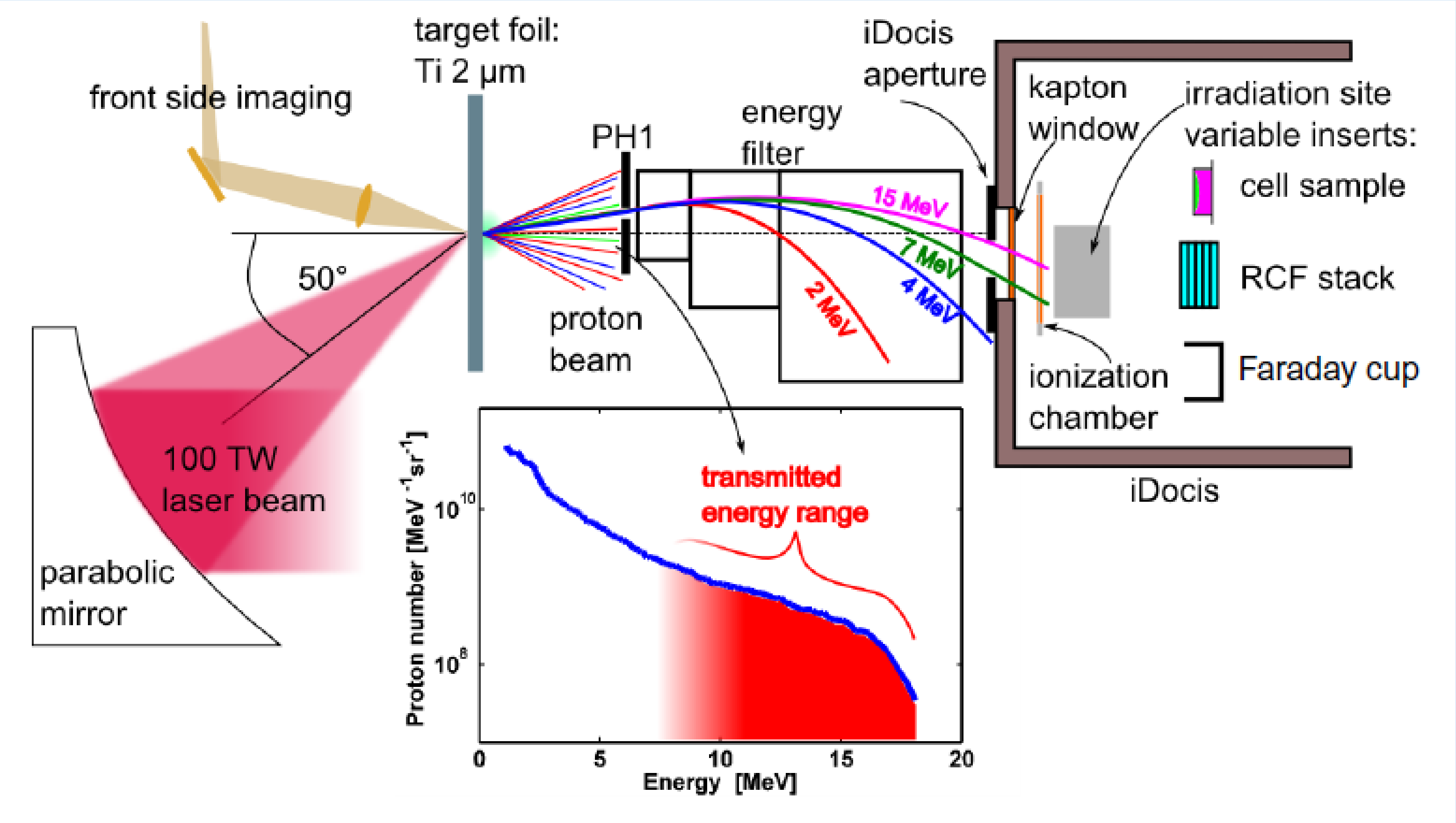
- **Proton therapy requires high quality proton beams**, i.e., beams with sufficiently small energy spread, ΔE/E << 1
  - Such a beam of laser-accelerated ions can be obtained using a double-layer target
  - The first (front) layer consists of heavy ions with electric charge eZi and mass mi, followed by a second (rear) thin proton layer

- Similarly, a carbon-rich target can be used to produce carbon ion beams.



Laser accelerators

Irradiation of in vitro tumour cells with laser-accelerated proton pulses showing dose-dependent biological damage



S.D. Kraft et al., Dose-dependent biological damage of tumour cells by laser-accelerated proton beams, New Journal of Physics 12 (2010) 085003

Laser accelerators for therapy: requirements

A Proton Therapy beam has strict requirements to ensure optimal deposition of the prescribed dose, allow accurate dosimetry and verification of dose delivery, minimize the dose to areas outside the desired treatment volume, and assure patient safety from accidental overdoses

Issues to be considered for a future laser-based hadron-therapy system:

- Mature (cyclotrons and synchrotrons) versus emerging technology
- Beam energy (energy selection system)
- Energy variability and monochromaticity ($\Delta E/E \ll 1$)
- Beam intensity
- Lateral field definition
- Dose conformation to the target volume
- Dose accuracy and dosimetry
- Isocentric delivery
- Radiation protection and patient protection
- Cost

See: Ute Linz and Jose Alonso, What will it take for laser driven proton accelerators to be applied to tumor therapy? Phys. Rev. ST Accel. Beams 10, 094801 (2007)