The medical and industrial applications of cyclotrons

JUAS
Archamps, March 5th 2013

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Organization of the lecture

- Introducing Ion Beam Applications (IBA)
- Cyclotrons for the production of radioisotopes for medical diagnosis applications
- Cyclotrons for the production of radioisotopes for systemic radiotherapy and for the brachytherapy of cancer
- Replacing reactors for radioisotopes production
- Proton therapy
- Carbon therapy
- Latest developments: the S2C2
- Industrial applications

Belgium has an old tradition of cyclotrons

- Belgium is one of the first European country to install a cyclotron in 1947…as a result of Uranium ore mining in Katanga during WW2
- Cyclotron Research Centre at LLN in 1970.

Once upon a time…

- The story of IBA started when UCL team imagined to produce a cyclotron for the production of medical radioisotopes…
- Truly a revolutionary cyclotron, producing 5x more output and consuming 3x less energy than any existing cyclotrons…
- We searched, but no industry was interested to build our new cyclotron design…

The origins of IBA

- Therefore, IBA was founded in 1986, as a spin-off of the Cyclotron Research Center (CRC) of the Catholic University of Louvain in Louvain-la-Neuve (Belgium)

The origins of IBA

- The initial company ambitions were modest:
  - Build one cyclotron per year
  - Maximum 15 employees
  - Business of 1.5 to 2 M€ per year
  - Getting rich was not part of the initial objectives, but having fun clearly was…
  - …and in this respect, we were quite successful !

The IBA Group in 2010

- 2,050 employees in 40 sites on 3 continents
- Turnover > 330 M€, growing 25% per year
- More than 300 systems (200 Cyclotrons) installed
- Not anymore a cyclotron company, but a company focused on the fight against cancer:
  - Diagnostic: molecular imaging
  - Therapy: Particle therapy & dosimetry

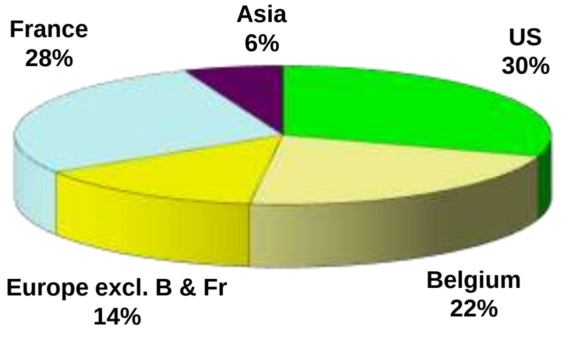
IBA → 2006 → iba

IBA Group Structure: 2050 Employees Worldwide

Corporate: 138

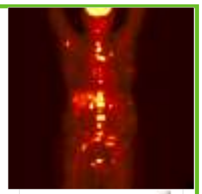
Finance, HR, Legal, R&D, Communication, QA

Molecular	TG	Dosimetry	Bio Assays	PT	CS	Industrial
1094	305	159	150	120	55	29



IBA Today: Centering on the fight against cancer

Pharmaceuticals



Radiopharmaceuticals
- Molecular Imaging
- Nuclear Medicine (diagnostics & therapy)

Bioassays
- In vitro medical diagnostics
- Drug screening

Particle Therapy

Proton Therapy is increasingly considered as the ultimate radiotherapy for cancer due to its superior dose distribution

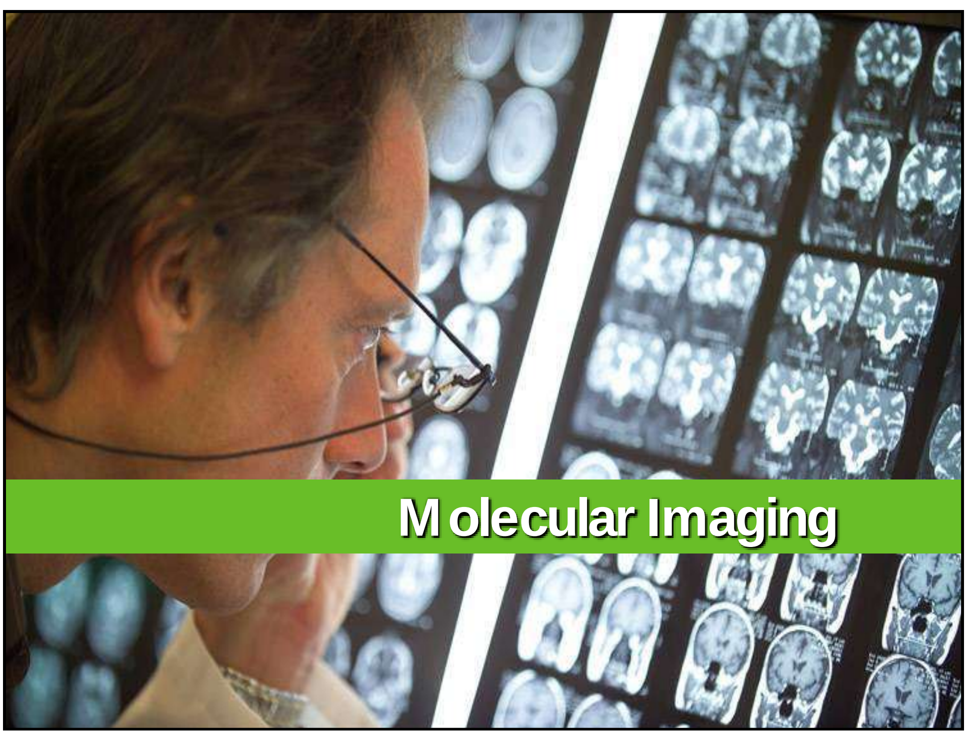
Dosimetry

Dosimetry equipment
to measure radiation dose for
- Radiotherapy
- Radiodiagnostics

Accelerators

Cyclotrons
- To produces Radioisotopes

E-beam / X-rays
- To irradiate / treat many industrial products



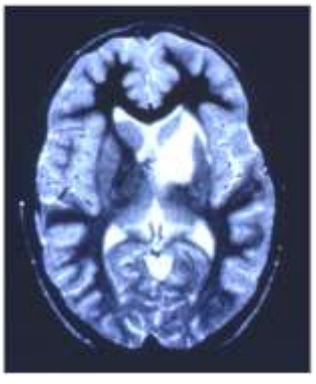
Molecular Imaging

The use of Radio Isotopes for medical imaging

- Radio tracers can be used to label a specific chemical molecule.
- They allow to see metabolism, while X-ray scan or MRI are better to see the anatomy .
- Nuclear medicine (imaging of metabolism using molecules labeled with an appropriate radioisotope) is therefore not in competition, but in complement of imaging techniques such as X-ray, X-ray scan or MRI.

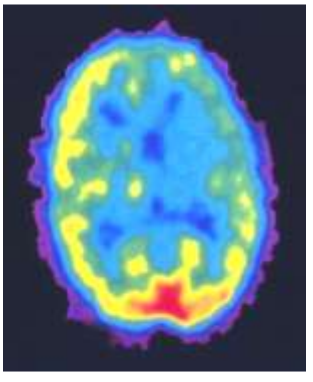
Metabolic vs. anatomic imaging

MRI



Anatomic View

PET



Biological Function

Metabolic vs. anatomic imaging

How is imaging done with radio-tracers ?

Single photons isotopes

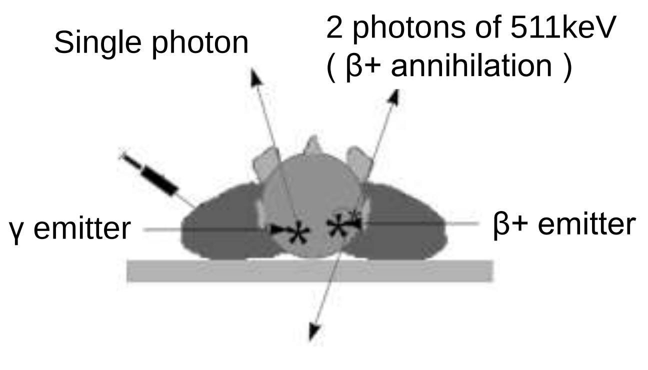
- The imaging of single photons emitters requires:
  - a collimator (causes a loss of efficiency !).
  - a position-sensitive detector (with good detection efficiency): the Anger camera.
- The image obtained is a projection.
- Multiple projections can be mathematically correlated to produce a 3D representation.
- SPECT (Single Photon Emission Computed Tomography).

How is imaging done with radio-tracers ?

Positron emitting radio-isotopes

- The emitted positron travels a few millimeters, then meets an electron and annihilates, emitting two anti-parallel photons of 511keV.
- These two photons can be detected in coincidence by a ring of detectors surrounding the region of interest.
- One knows then that the source of activity is on the line connecting the two detectors.
- Several detections allow to locate the source.
- By mathematical reconstruction, a 3D representation of the activity can be obtained.
- PET (Positron Emission Tomography).

How is imaging done with radio-tracers ?



How to select a good single photon radio-tracer ?

The photon energy

- Low enough to keep a good detector efficiency.
- High enough to cross the body tissue.
- 100 keV $\leq$ E $\leq$ 300 keV is the optimum.

How to select a good single photon radio-tracer ?

The half-life

- Short enough to minimize the patient's exposure.
- Long enough to allow industrial production and distribution to the hospitals.
- Practically 10h $\leq$ T1/2 $\leq$ 100h is best.
- Generators are great too !

example

^{99}Mo (66 hours) = ^{m99}Tc (6 hours)

^{81}Rh (4.6 hours) => ^{81}Kr (13sec)

How to select a good single photon radio-tracer ?

The chemistry

- The radio-tracer should bind easily the organic molecules of interest.

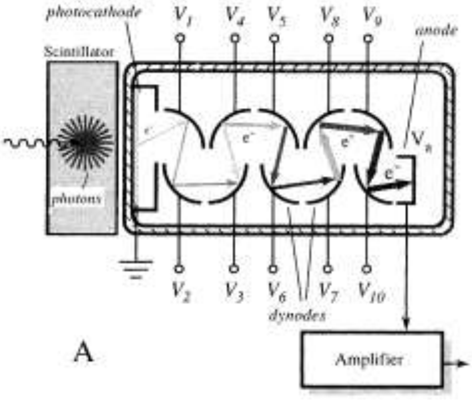
example

++ Halogens, Technetium are good

++ Noble metals (Gold) are bad

Detecting the radiation

Scintillator with photomultiplier tube



The incoming gamma ray interacts with the scintillator to produce photons. These photons dislodge electrons from the photocathode in the photomultiplier tube. These electrons are accelerated to the first nearest dynode where they dislodge further electrons. This process continues down the tube, resulting in a cascade of electrons.

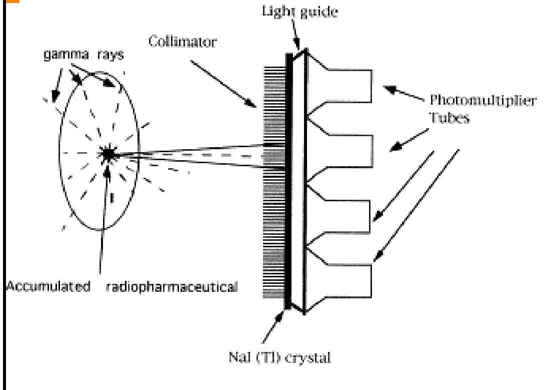
Detecting the radiation

Scintillator with photomultiplier tube

The SPECT gamma camera (Anger camera)

Anger camera

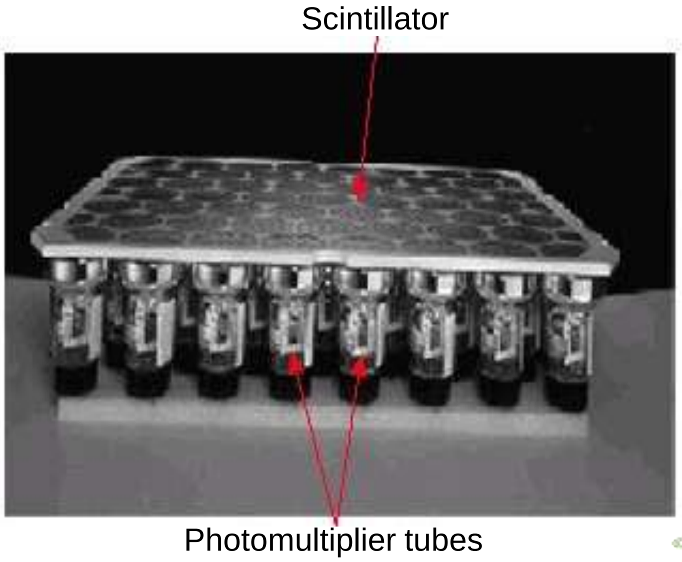
The collimator prevents photons that are not approximately perpendicular to the collimator holes from interacting with the detector.



The field of view for the detector element behind each hole of the collimator is divergent, so that in a gamma camera, spatial resolution degrades as the distance to the distance to the object is increased. Collimators are usually made of lead.

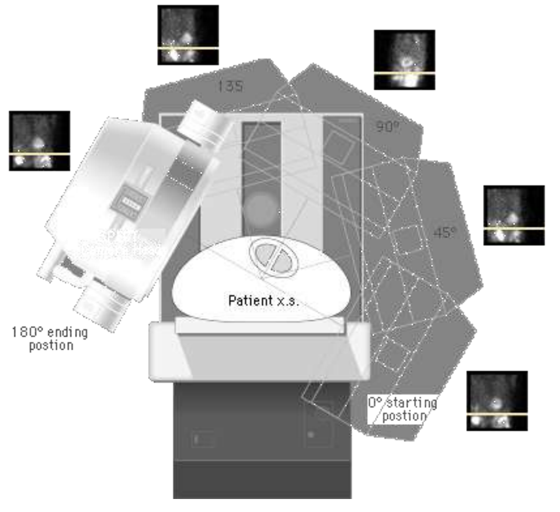
Typical dimensions: holes 3mm, walls 1mm, depth 40mm.

The SPECT gamma camera (collimator removed)



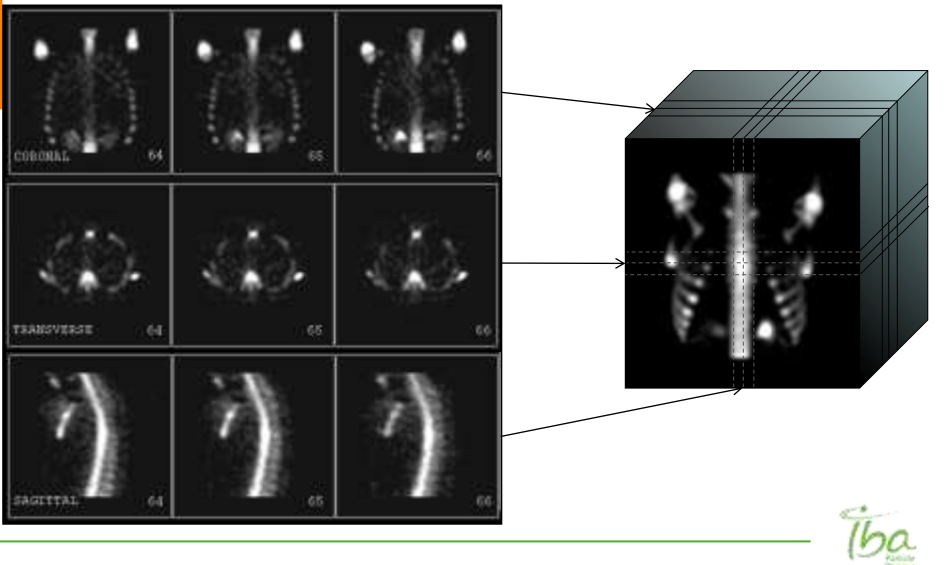
The SPECT gamma camera

The SPECT gamma camera



The SPECT gamma camera

3D Reconstruction



Nuclear reactions for Radio-Isotopes production

- Neutron capture, as well as fission is performed in nuclear reactors.
- To bring a positive charged particle into a nucleus requires to overcome the Coulomb barrier and requires therefore the use of accelerators.
- The compound nucleus formed is unstable, and immediately cools off by emitting neutrons or alpha particles (more rarely protons).
- Typical reactions are: (p, xn) , (p, a) , (d, xn)….

Nuclear reactions for Radio-Isotopes production

Radioisotope	Half-life	Reaction	Energy (MeV)
^{201}Tl	73.1 h	^{203}Tl (p,3n) => ^{201}Pb => ^{201}Tl	17~28
^{67}Ga	78.3 h	^{68}Zn (p,2n) => ^{67}Ga	12~28
^{111}In	67.4 h	^{112}Cd (p,2n) => ^{111}In	12~28
^{123}I	13.2 h	^{124}Te (p,2n) => ^{123}I	20~25
		^{124}Xe (p,2n) => ^{123}Cs => ^{123}I	20~30
		^{124}Xe (p,pn) => ^{123}I	
		^{127}I (p,5n) => ^{123}Xe => ^{123}I	45~68

“Traditional” nuclear medicine

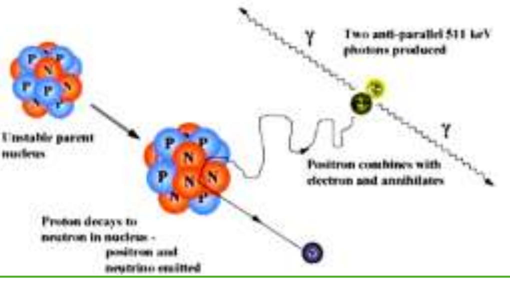
- Technetium 99m, the most commonly used radio-isotopes in nuclear medicine is produced in reactors.
- But a number of other, very important nuclear medicine radio-isotopes are produced with cyclotrons of higher energy.
  - ^{201}Tl (Cardiac studies).
  - ^{123}I (Thyroid, Various examinations).
- For these longer life isotopes, international distribution is possible.
- Large, very powerful cyclotrons are owned by radiopharmaceutical companies.

The Cyclone 30

The cyclotron used by all radiopharmaceutical producers

The positron (anti-electron)

- Proton rich nucleus decays: proton → positron + neutrino.
- Positron cools off by Coulomb interaction with electrons.
- At thermal energy: positron annihilates producing two anti-parallel 511keV photons. (within 4mrad due to momentum conservation)
- The finite positron range and the non-collinearity of the annihilation photons give rise to positional inaccuracy (±5mm).



The PET scanner

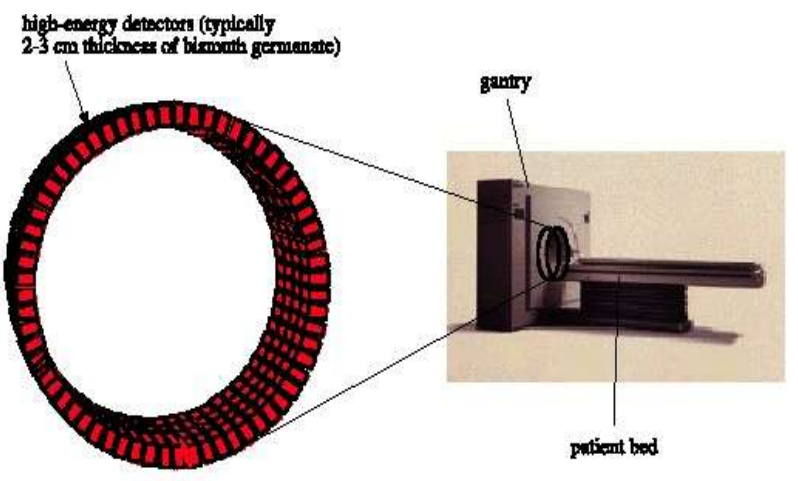
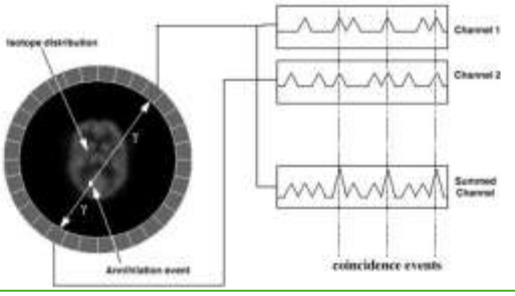


Figure 6. A dedicated PET system (photograph courtesy of CTI, Inc.).

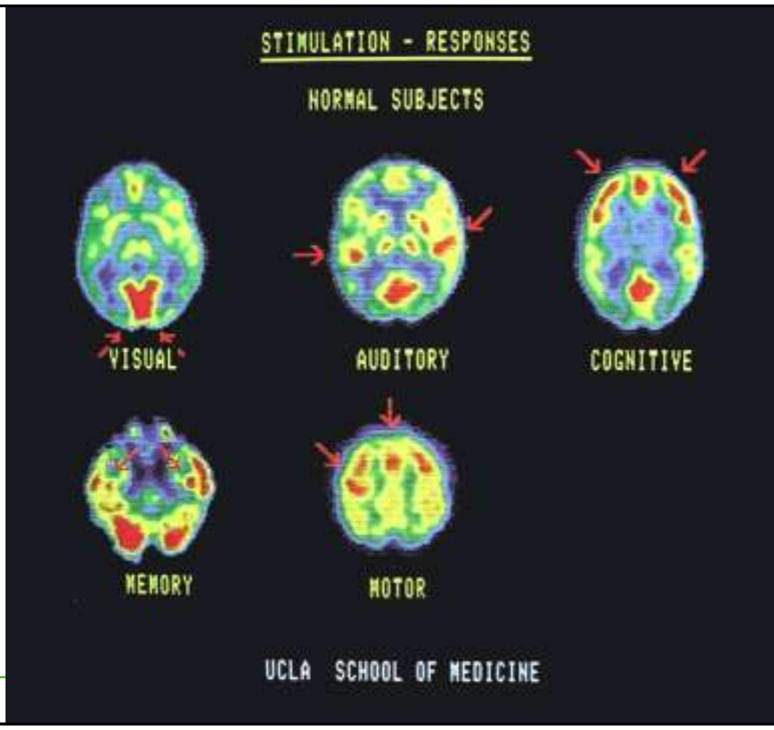
Coincidence detection in a PET scanner

In a PET camera, each detector generates a timed pulse when it registers an incident photon. These pulses are then combined in coincidence circuitry, and if the pulses fall within a short time-window, they are deemed to be coincident. A coincidence event is assigned to a line of response joining the two relevant detectors. In this way, positional information is gained from the detected radiation without the need for a physical collimator.

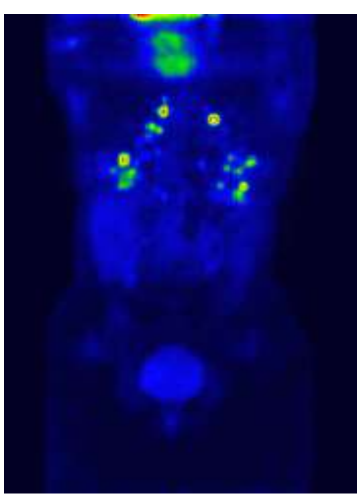


Positron emitting radioisotopes for PET

Radioisotope	Half-life (min)	Positron energy (MeV)	Reaction	Energy (MeV)
^{11}C	20.4	1.0	^{14}N (p,a)=> ^{11}C	5=>16
^{13}N	9.96	1.2	^{16}O (p,a)=> ^{13}N	8=>16
			^{12}C (d,n)=> ^{13}N	3=>8
^{15}O	2.07	1.7	^{15}N (p,n)=> ^{15}O	5=>14
			^{14}N (d,n)=> ^{15}O	3=>8
^{18}F	109.8	0.6	^{18}O (p,n)=> ^{18}F	5=>14



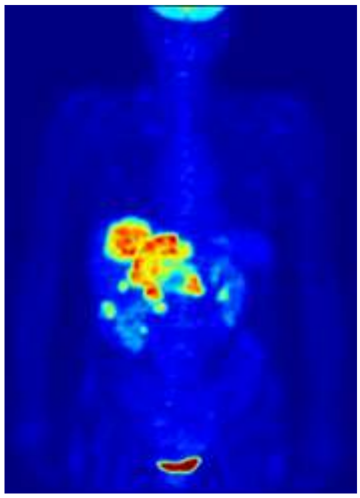
Cancer imaging with PET



^{18}F FDG

- 45 minute scan time
- normal liver & renal
- normal bladder
- metastatic lung lesions

Cancer imaging with PET



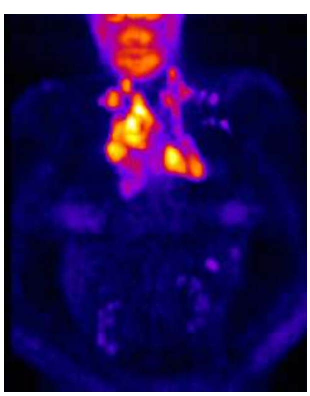
^{18}F FDG

- 45 minute scan time

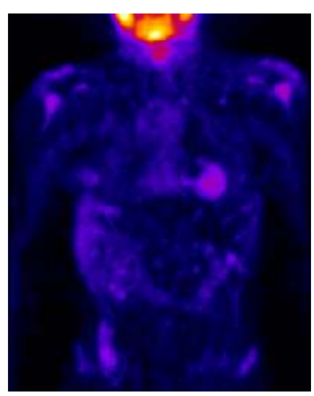
- normal heart, bladder.
- normal kidney, brain.
- colorectal tumor.
- metastatic liver lesions.

PET Scan - Response to Therapy

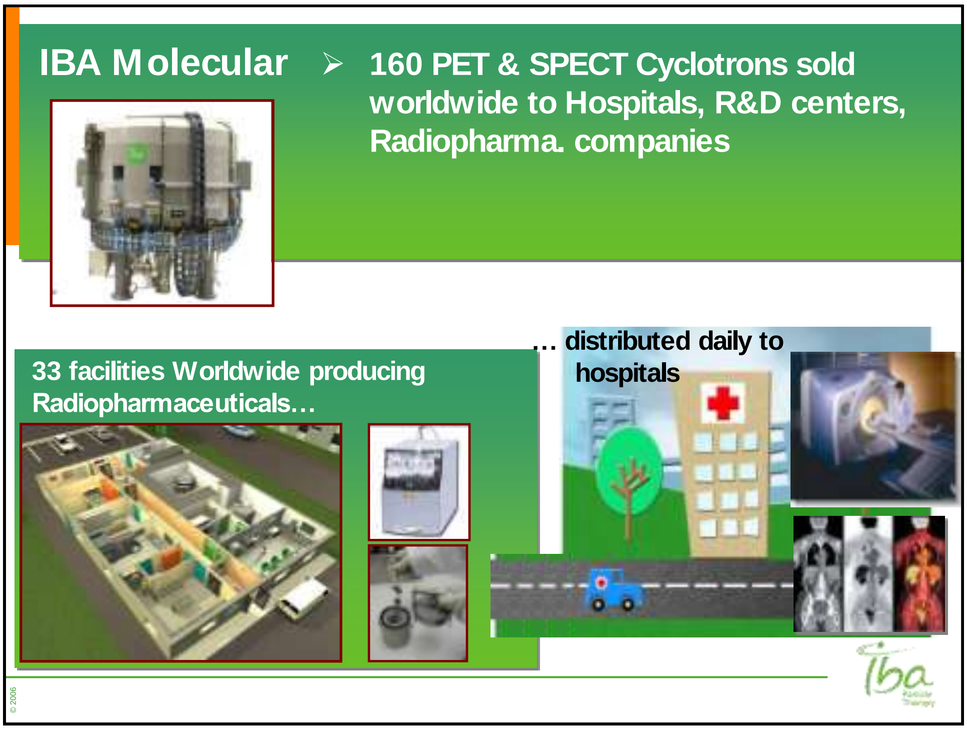
31 yo female with newly diagnosed Non-Hodgkin's Lymphoma

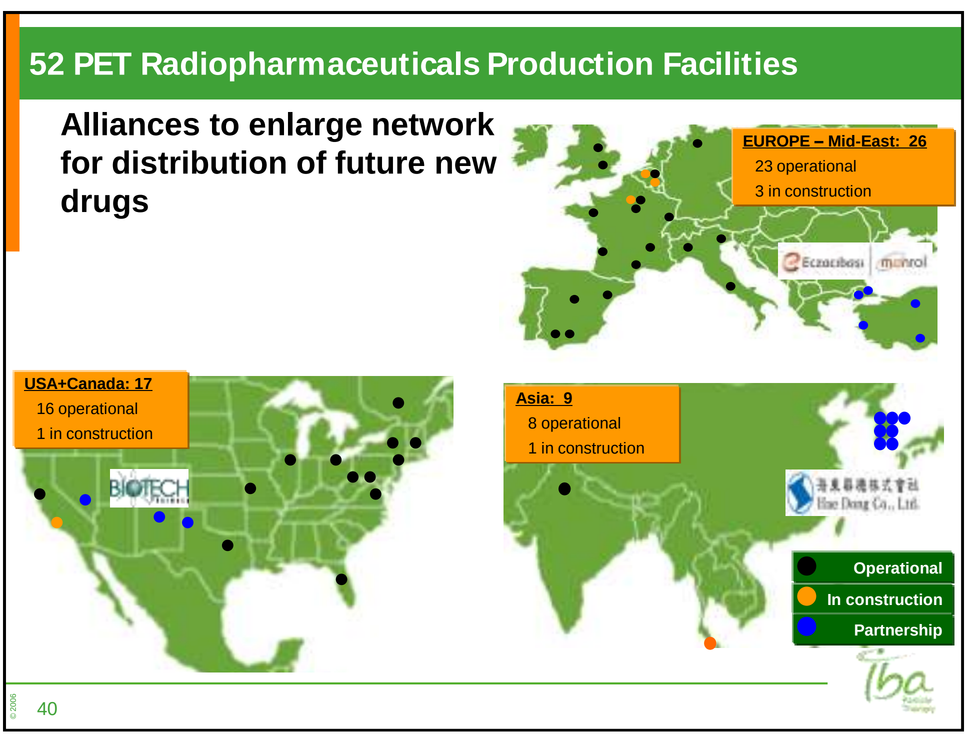


Staging PET Scan



Post Chemotherapy


IBA Molecular
160 PET & SPECT Cyclotrons sold worldwide to Hospitals, R&D centers, Radiopharma. companies
33 facilities Worldwide producing Radiopharmaceuticals…
… distributed daily to hospitals
© 2006
iba


52 PET Radiopharmaceuticals Production Facilities
Alliances to enlarge network for distribution of future new drugs
EUROPE – Mid-East: 26
23 operational
3 in construction
Eczacibasi
monrol
USA+Canada: 17
16 operational
1 in construction
BIOTECH
Asia: 9
8 operational
1 in construction
Operational
In construction
Partnership
© 2006
40
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Cancer therapy with Radio-Isotopes

Systemic cancer therapy with RI

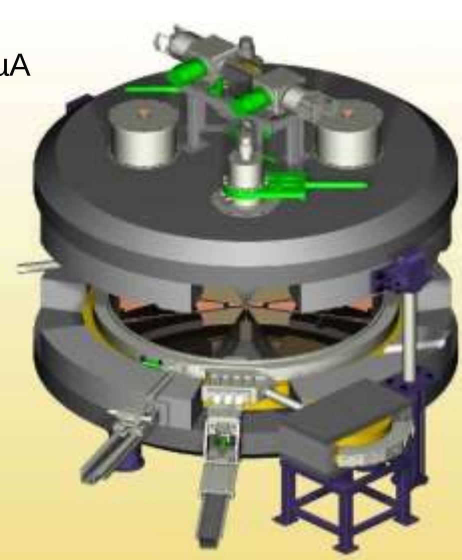
- When the cancer is not limited to a well defined, primary tumor, systemic therapies must be used.
- One well known solution is to graft a therapeutic (toxic) radio-isotope on a cancer cell seeking molecule.
- Alpha or Auger electron emitting radio-isotope are often preferred.
- The main problem is the dosimetry and treatment planning: how to assess correctly the radiation dose received by the tumor and by the healthy organs at risk.
- Pairs of diagnostic / therapy radio-isotopes are useful in this respect.

Pairs of radioisotopes

Diagnostic (PET) RI	Therapy RI
^{124}I	^{131}I
^{86}Y	^{90}Y
^{64}Cu	^{67}Cu
Etc!	

New high energy isotope research machine

- **Cyclone 70 for Arronax (Nantes, France)**
  - Proton 35~70MeV 750µA
  - Deuterons 17~25MeV, 50µA
  - Alpha 70MeV (fixed) 35µA
  - HH+ 35MeV(fixed) 50µA
- **Main research goals**
  - ^{211}At, alpha emitters
  - ^{67}Cu, ^{177}Lu, beta emitters
  - Pulsed alpha (research)



New high energy isotope research machine

The Nantes cyclotron in September 2010

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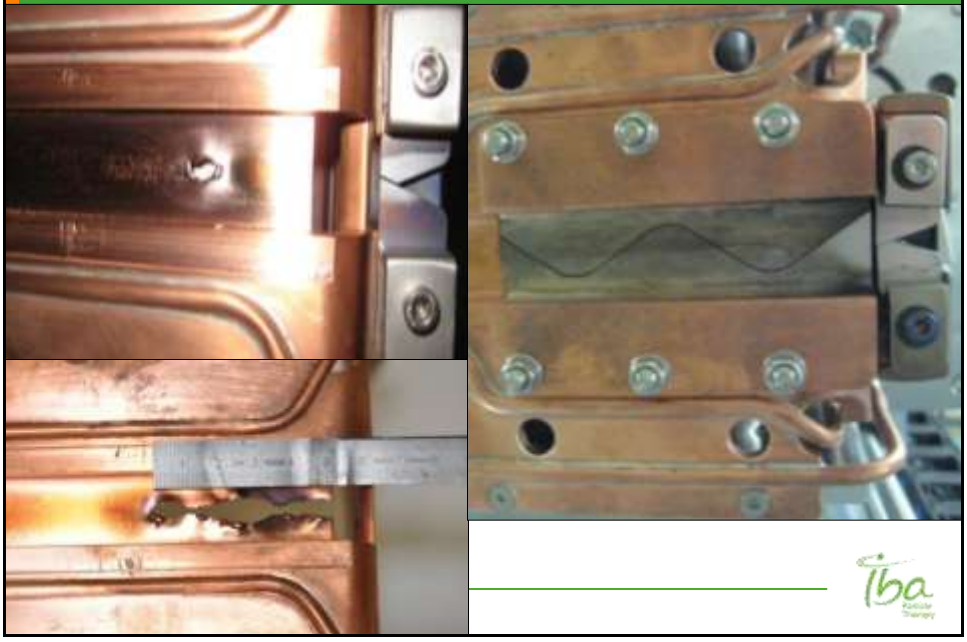
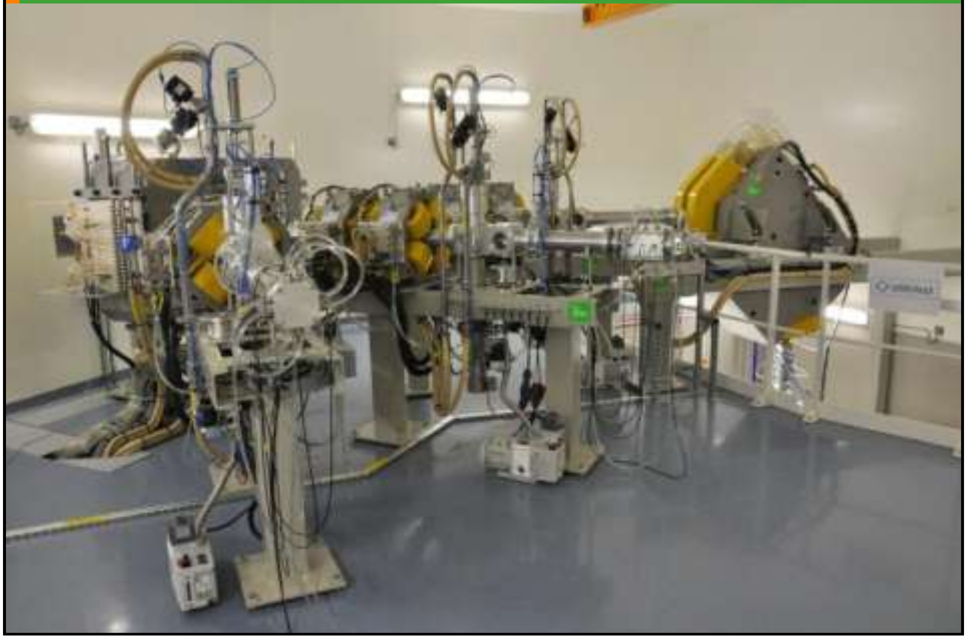


The Nantes cyclotron in September 2010



The Nantes cyclotron in September 2010

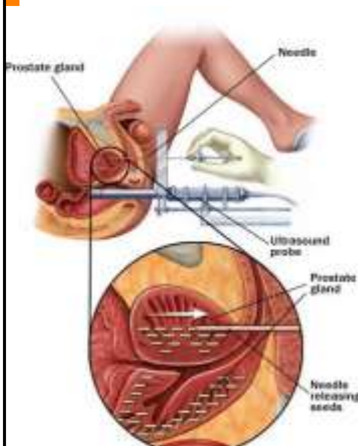
The Nantes cyclotron in September 2010

Brachytherapy

Local Eradication of a Tumor
by Radioactive Implants

Theragenics IBt

Prostate Brachytherapy



Pd-103 vs. I-125

	^{103}Pd	^{125}I
Half-life (days)	16.97	60
Energy (keV)	20~23	27~35
Half-value-layer (mm.Pb)	0.008	0.02
Biologic dose equ. (Gy)	115	160
Initial dose rate (cGy/hr)	20~24	6~10

Cyclotrons for brachytherapy

- Large doses, lower cross-section require high current operation
  Examples
  - 18Mev
  - 2mA on target
  - 14 cyclotrons in the same factory: 28mA total proton beam current
- In such cyclotrons, 80% of the RF power is used for beam acceleration, 20% for building the accelerating field
- Current total accelerator efficiency are over 35%, 50% efficiencies in view !

The C18+

30 kW of beam with 100 kW of electrical power

80% of the RF power is beam acceleration

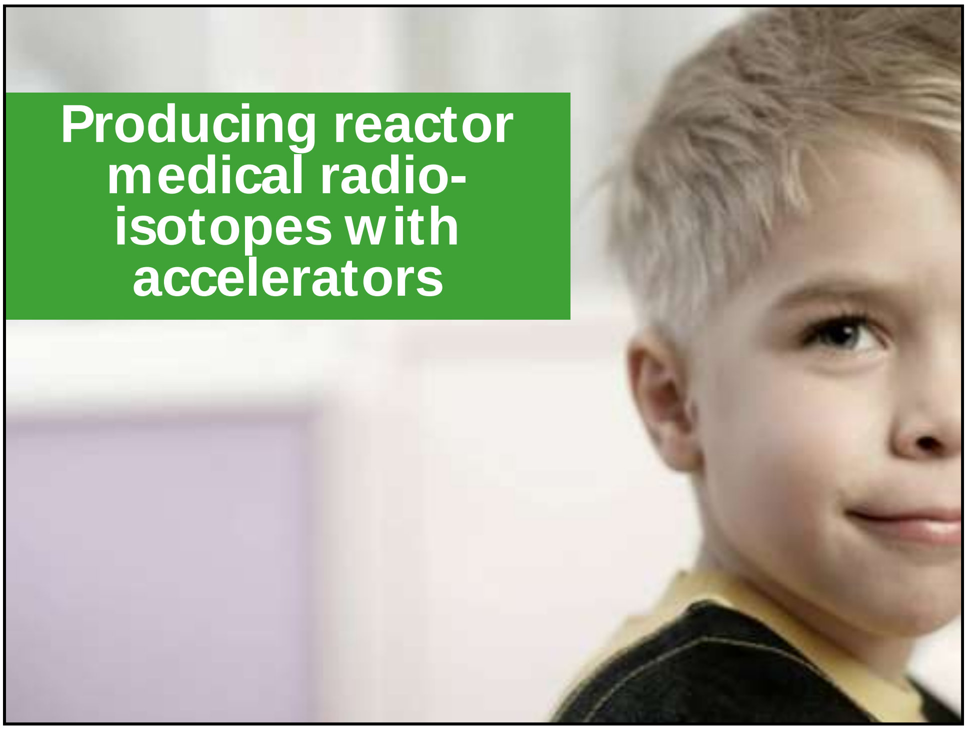
© 2006

The C14AE

Designed to deliver 10mA of 14MeV protons. The ion source reached 28mA on internal beam stop. Extracted beam intensities reached 1.4mA. Beam current on target reached 0.8mA.

© 2006

Producing reactor medical radio-isotopes with accelerators



The importance of the ^{99}Mo > ^{99m}Tc generator

- We know very well the production of radioisotopes by cyclotrons.
- But 80% of the radio-isotopes used in nuclear medicine are produced in nuclear reactors.
- Among these reactor produced radio-isotopes, the Technetium 99m (6 hrs), a decay product of Molybdenum 99 (66 hours) is the most commonly used radio-isotope in nuclear medicine.
- Every year, 36 million medical procedures based on Tc99m are conducted in the world. This not only is critical for the timely diagnostic of patients, but also represents more than 20 Billion USD in medical fees.

The production of ^{99}Mo

- ^{99}Mo can be produced by neutron capture on natural Mo (^{98}Mo = 24%). The process is simple and inexpensive, but yields a very low specific activity.
- High specific activity ^{99}Mo can be obtained by ^{235}U fission. 6% of the ^{235}U fission events produce a ^{99}Mo nucleus as a fission product. Targets are made Highly Enriched Uranium (HEU), with a progressive shift toward Low Enrichment Uranium (20% ^{235}U) (LEU).
- In today's production, aluminum targets containing 4g of HEU are irradiated for a week in high flux research reactors.
- After irradiation, the highly radioactive target is allowed to decay for one day, then is sent to the processing facility.

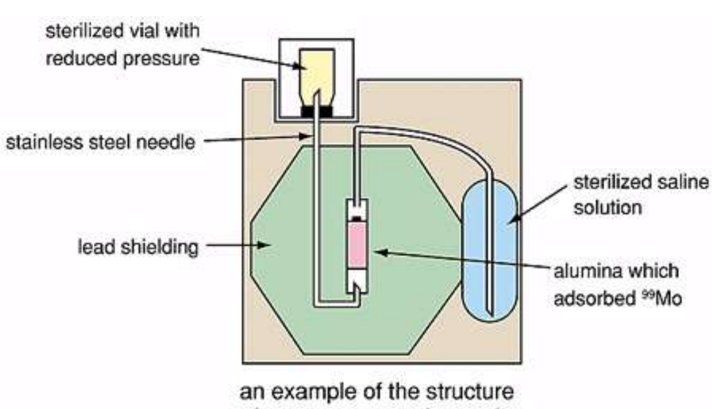
^{99}Mo processing

- The irradiated HEU targets (>40,000Ci !!!) are transported to the ^{99}Mo processing facility (Fleurus, Petten, Chalk River, Pelindaba).
- The targets are dissolved, and the selected fission products are chemically separated. Each target gives around 800Ci of ^{99}Mo EOI, or 135Ci post-calibrated 6 days.
- The world weekly production is 8,000 to 10,000Ci, p.c. 6days. USA and Western Europe use most of this.
- So each week, about 60 targets are irradiated worldwide
- The purified ^{99}Mo is sent in bulk form to the producers of generators.

The ^{99}Mo -> ^{99m}Tc generator

- For the distribution to the final customer, the ^{99}Mo solution is fixed on a small ion exchange alumina column.
- The ^{99}Mo (66 hours) decays continuously into ^{99m}Tc. Because of it's different chemical properties, the ^{99m}Tc is not stably fixed on the alumina column.
- When needed, the user washes the ^{99m}Tc out of the ion exchange column with a sterile saline solution.
- The ^{99m}Tc is used to label a molecule which will target the body site to be studied.
- ^{99}Mo -> ^{99m}Tc generators are produced by radiopharmaceutical companies and distributed to hospitals or radio-pharmacies on a weekly basis.

A typical commercial ^{99m}Tc generator



an example of the structure
of a generator on the market

Some economic data

- A nuclear medicine or PET examination is generally charged 500 to 1500€ to the patient or to the social security.
- A patient dose of cyclotron produced RI is generally sold to the hospital 150 to 300€.
- In contrast, the cost to the hospital of a patient dose of ^{99m}Tc is generally less than 15€ (but this cost is rising). In this price, the cost of the neutron irradiation of the target is today less than 1€.
- Reactor produced isotopes, such as ^{99m}Tc are therefore much less expensive than cyclotron produced radio-isotopes.

The present crisis (1)

- The neutron irradiation of HEU targets for the production of fission products for medical application is made in a small number of aging research reactors.
- All the production for North America is done on NRU a very old research reactor in Chalk River (Canada). NRU was put in operation in the early 50's!
- In Europe, the production is done on a small number of aging research reactors: HFR (Petten), BR2 (Mol), Osiris (Saclay).
- Production reactors are also found in South Africa (SAFARI) and Australia (OPAL).

The present crisis (2)

- The present reactors used for medical RI production are research reactors, paid by public money to do research on nuclear technology.
- RI production is not their primary mission, and is charged at marginal (minimal) cost. The cost paid today for irradiation in state-sponsored reactors is so low that the construction of new reactors for medical RI production cannot be financed.
- These research reactors are characterized by cycles of operation of a few months, separated by long maintenance periods.
- Most of these reactors have vastly exceeded their design lifetime.
- Construction of new research reactors is unpopular. Only the Jules Horowitz reactor is being built by the CEA. It is expected for 2015…2017

The present crisis (3)

- 10 years ago, Nordion, the world largest ^{99}Mo producer, ordered from AECL the construction of two new reactors for the production of medical RI: the Maple-X reactors
- But the design of the Maple-X reactor was flawed, and at the first tests, the new reactors exhibited a positive temperature coefficient for the reactivity. They were never allowed to operate
- After 10 years of efforts, and more than 600 Mcan$ spent, the Canadian government decided to abandon the Maple X reactors?

The present crisis (4)

- In 2009, both HFR (Petten) and NRU were closed after leaks were discovered in the primary loop of the reactor
- HFR was authorized to restart for a limited time, but NRU is still stopped. NRU is expected to restart in April, but HFR will be stopped again for a long maintenance
- Osiris will be definitely reach the end of its life in the coming years, hopefully it will operate till the start of the JHR
- As a result, the distribution of ^{99}Mo -> ^{99m}Tc generators was seriously disturbed last year. The situation is not going to improve !

What can we do?

- What do you do when ^{99}Mo from reactors becomes unavailable?
- You ration the use of generators between your customers (done today)
- You can substitute cyclotron produced RI at a much higher cost (done today)
- You can produce directly ^{99m}Tc from a p-2n reaction on ^{100}Mo with a PET or SPECT cyclotron (M. Lagunas Solar, UC Davis). The yield is OK (10 Ci/hour at 21MeV, 500µA) but logistics and costs are similar to ^{18}F production
- You could also (theoretically only) produce ^{99}Mo by a p-p,n reaction on ^{100}Mo, but the yield is terrible.

ADONIS is a possible solution

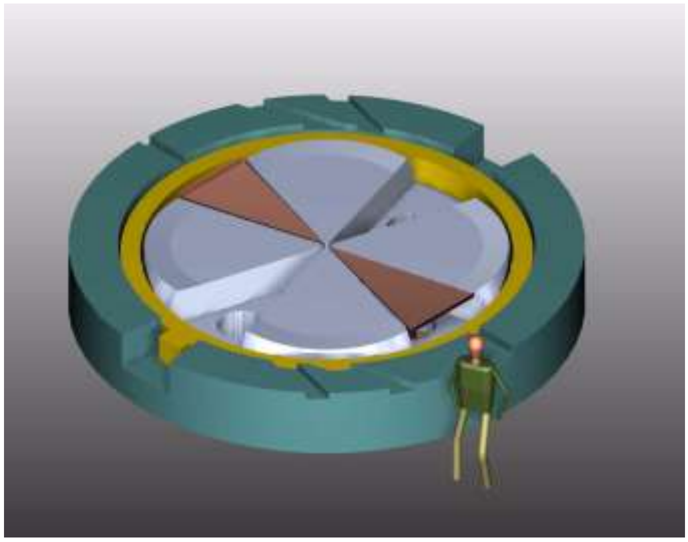
- ADONIS stands for Accelerator Driven Optimized Nuclear Irradiation System.
- Joint research between SCK-CEN, IRE and IBA.
- V1 (1995): 150MeV x 2mA = 300kW of proton beam.
- Converted in a tantalum target to $7.5 \times 10^{+15}$ neutrons/second.
- These neutrons produce 700kW of fission power in standard HEU isotope production targets surrounding the neutron target.
- Weekly production of 5000Ci of ^{99}Mo (pc 6 days EOI).
- Project unfortunately freezed (again!).

- http://accelconf.web.cern.ch/accelconf/e96/PAPERS/ORALS/THO07A.PDF

The main elements of ADONIS

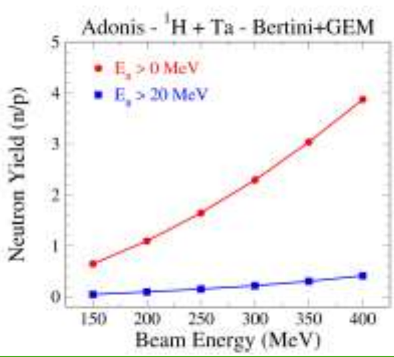
- A 150MeV, 2mA cyclotron, using H- acceleration and extraction by stripping, as the C30 and ARRONAX.
- A beam line bringing the extracted beam vertically up to a subcritical assembly located in another vault.
- A Tantalum target converting the proton beam into neutrons by spallation.
- An assembly of standard isotope production HEU targets arranged in water around the neutron source.

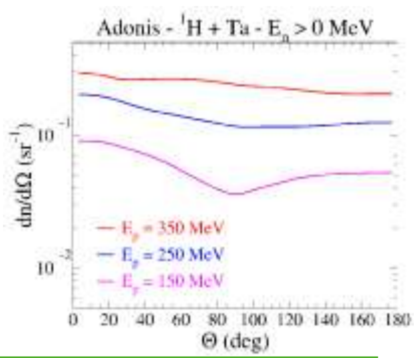
Lower pole



Tantalum Spallation Target

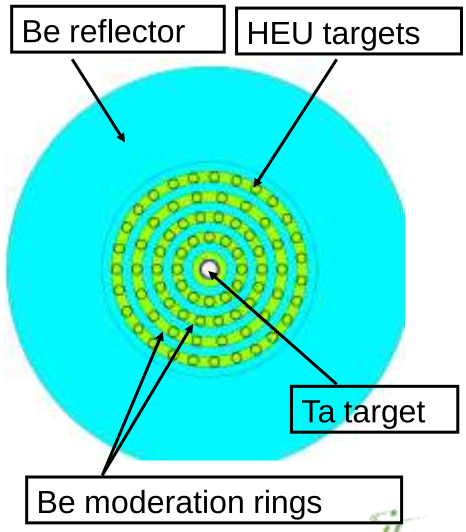
- Study of secondary neutron emitted by ^{1}H + Ta using MCNPX / PHITS
- Thick target yield increases rapidly with beam energy.
- Emitted neutrons are mostly evaporation neutrons <20MeV.
- These neutrons are isotropically emitted by the target.



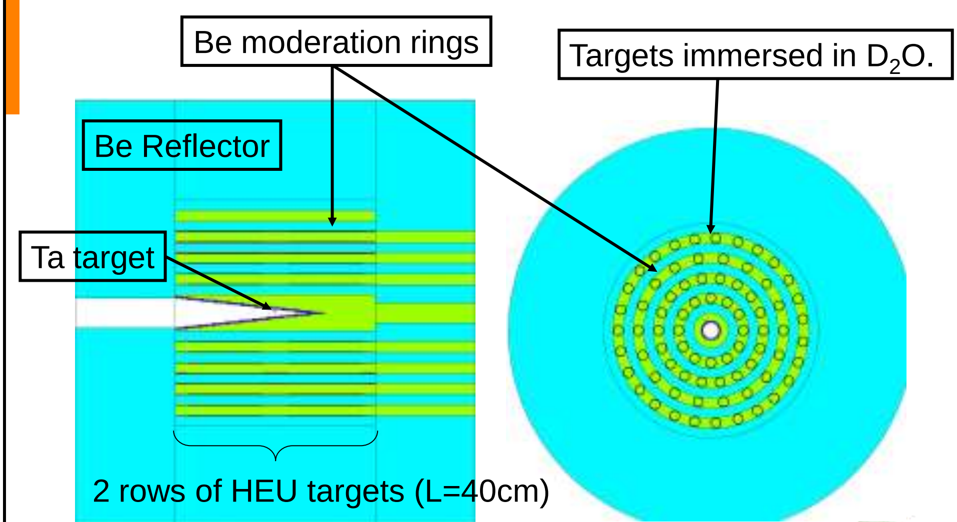


Sub-critical assembly Design (1)

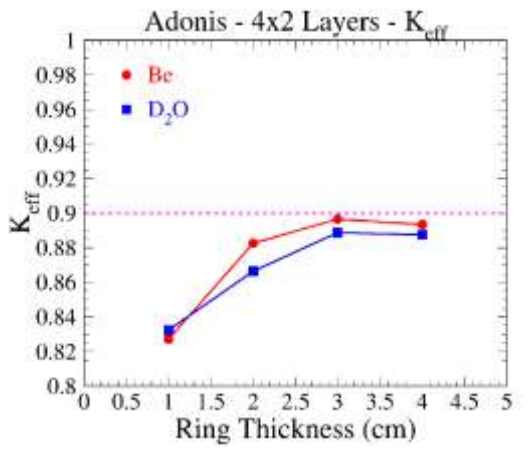
- Conical Ta spallation target.
- Design based on cylindrical targets as used today.
- Beryllium moderation rings between target layers.
- HEU targets (4g) in D_2O.
- Be reflector (20 cm thick).
- Targets on 4 cylindrical layers, each layer being made of 2 rows of targets: total of 150 targets.



IBA Design (2)

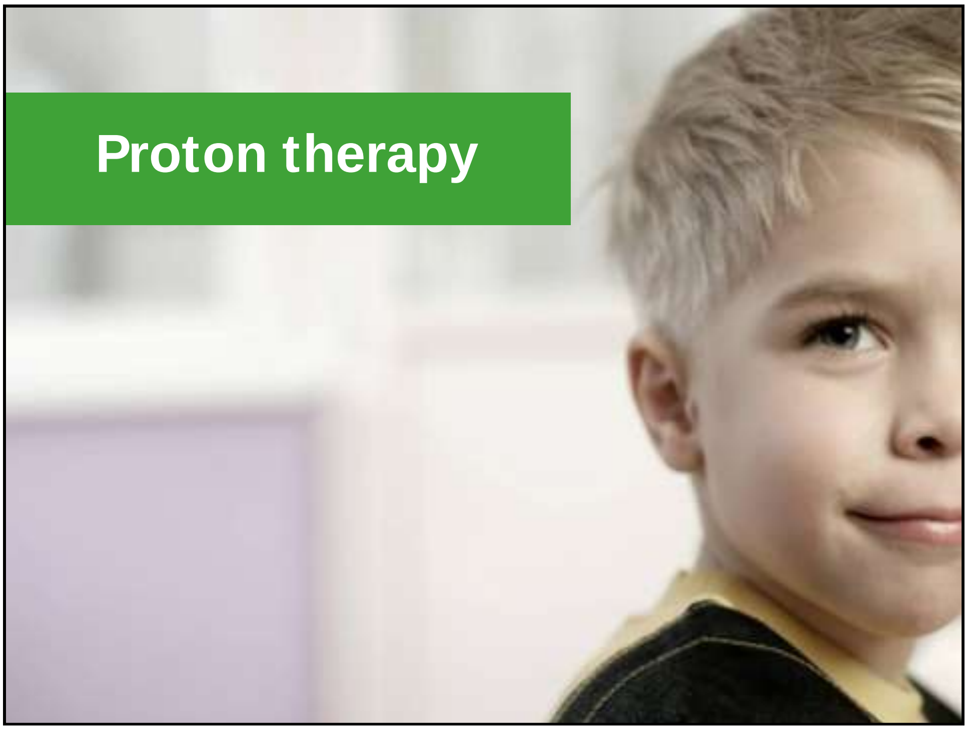


Criticality Calculations

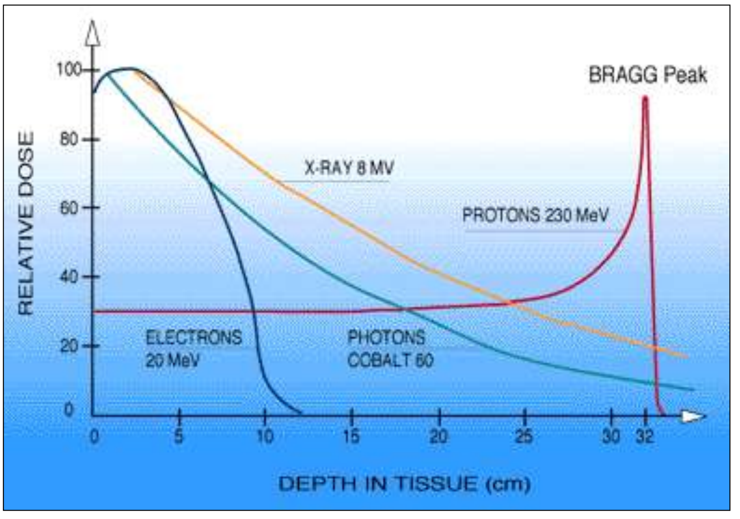


➔ K_{eff} remains below 0.9

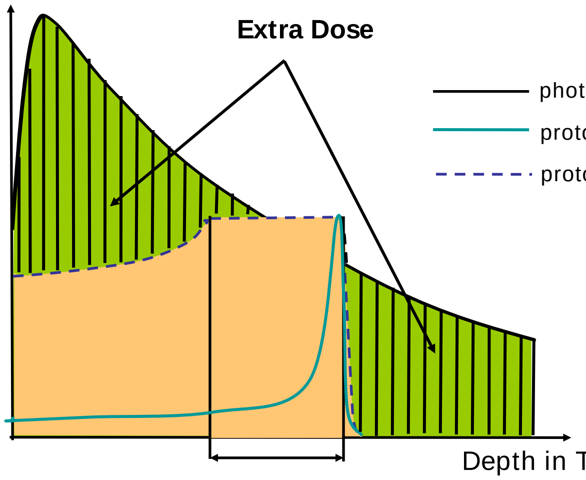
Proton therapy



The depth dose curve distributions

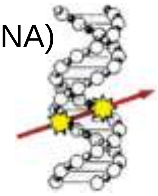


Photon-Proton dose distribution comparison

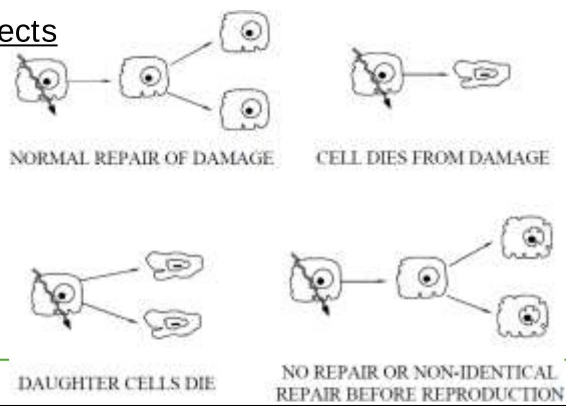


Radiobiological effects of ionizing radiation

- **Complex mechanism depending on many factors.**
  - Type and state of irradiated cells (O_2, SS or DS DNA)
  - Type and energy of incident radiation (LET)
  - Quantity of radiation per volume (dose)



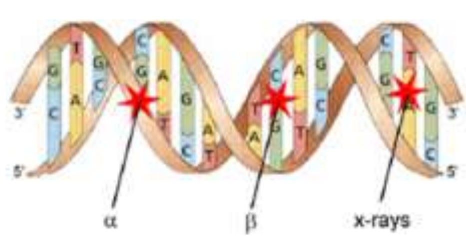
Possible effects



Radiobiological effects of ionizing radiation

- **There are two types of radiation damage:**

  Direct: High LET particles (α, slow n, p or β) have frequent interaction over a short distance; they break directly DNA strands due to massive but local destruction. Whatever the state of the cell, enzymes generally cannot repair the DNA.

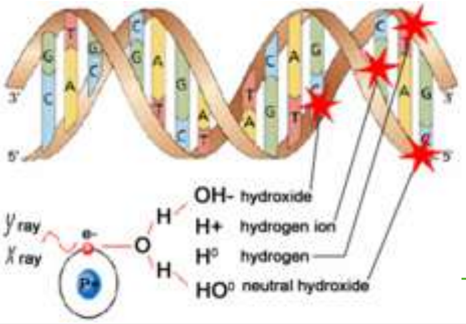


Radiobiological effects of ionizing radiation

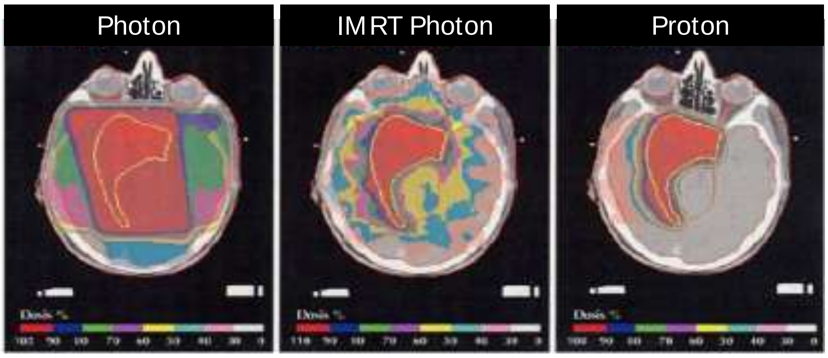
- **There are two types of radiation damage:**

  Indirect: Low LET particles or radiation (γ, X-rays, fast n, p or β) induce radiolysis in the cell. The very chemically reactive free radicals destroy a DNA strand. The presence of O_2 increases the production of free radicals, therefore the radiosensitivity of the cells to low LET radiation.

  Indirect effects are dose and state of cell dependant.



Particle Therapy: Comparing PT & Conventional RT

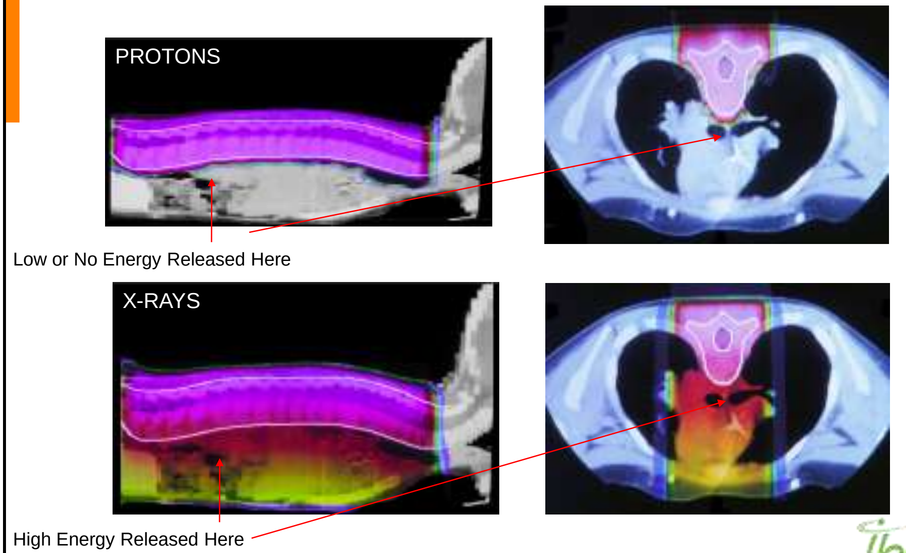


Conventional Radiotherapy

IMRT = Intensity Modulated Radio Therapy

Scattering technique

Medulloblastoma Treatment X-Rays vs Protons



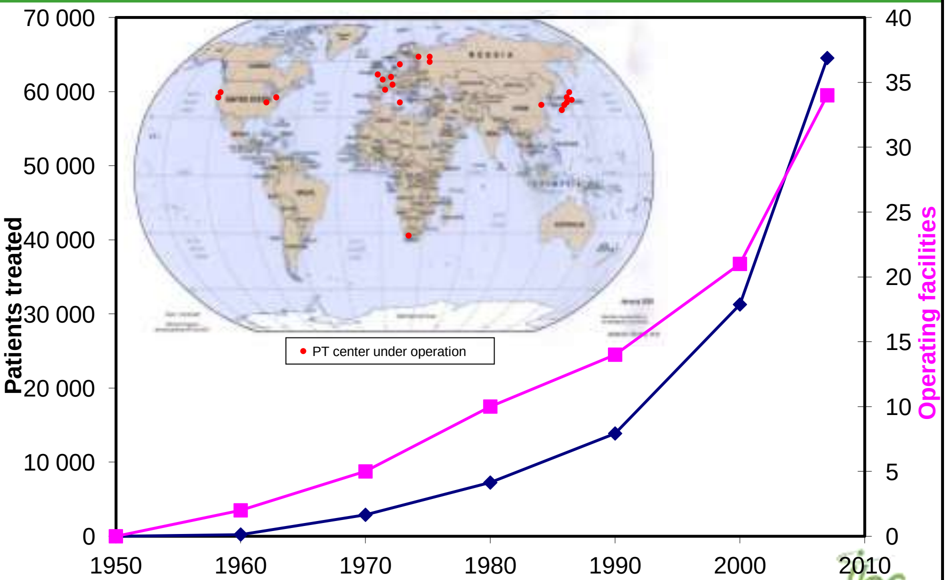
Proton therapy center

€30-55 millions for equipment
€45-100 millions for the center

IBA Proton Therapy System

- A Proton therapy system is much more than an accelerator.
- It is a complex, multi-room system, filling a Hospital building.
- The treatment rooms are larger than the cyclotron vault.
- The total investment is around 100 M€, of which 45 M€ for the equipment.
- A PT facility can treat 1500 patients/year and can generate revenues in excess of 30 M€/year!

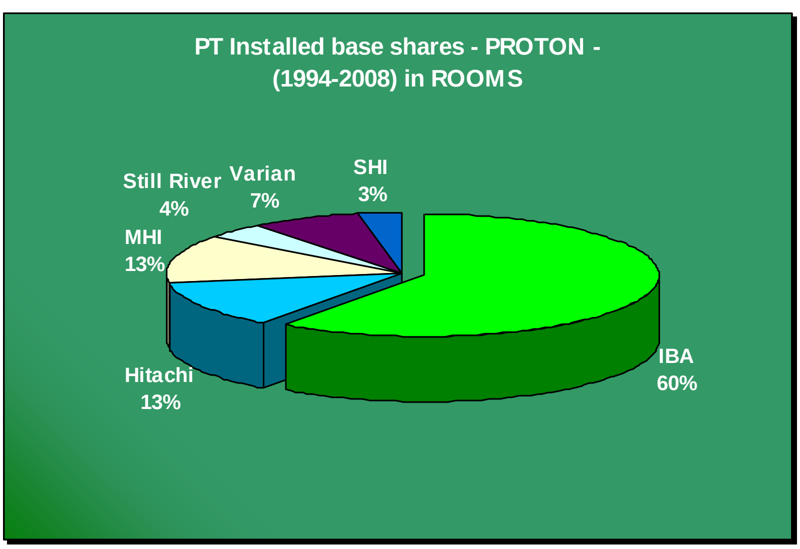
Proton Therapy is growing rapidly !



Courtesy Janet Sisterson & PTCOG

More than 20 IBA PT customers in the world

IBA has currently the largest installed base in PT



An IBA proton therapy treatment room

An IBA proton therapy treatment room

UFPTI, Jacksonville, USA

- Construction start date: Mar 2004
- PT equipment installation start: Mar 2005
- 1st Patient : Aug 2006 !
- today : 120 patients/day treated in 3 Gantry rooms
- 3 Gantry Rooms + 1 Eye Treatment Room

The UPHS Particle Therapy Centre, Philadelphia

- The largest Particle Therapy centre to date!
- 4 Gantry Rooms
- 1 Fixed Beam Room
- 1 Experimental Room
- Beam since July 2008

Westdeutsche Protonentherapiezentrum, Essen

- First Particle Therapy centre based on a Public Private Partnership (PPP) model
- 3 Gantry Treatment Rooms
- 1 Double Fixed Beam Room with Eye Treatment line
- Beam since September 2008

New cyclotron and gantry for CPO in Orsay

- New equipment for an existing PT center
- 1 new Gantry Room
- 2 existing Fixed Beam Rooms
- Building competed, cyclotron and gantry on site

Hampton University Proton Therapy Institute

- 4 Gantry Rooms
- 1 Fixed Beam Room
- Building almost competed, equipment being shipped

IBA PT subsystems : the Cyclone 235

The 230MeV cyclotron. MGH, Boston, 2000.

IBA PT subsystems : the Cyclone 235

The 230MeV cyclotron. WPE, Essen, 2010.

IBA PT subsystems : the Cyclone 235

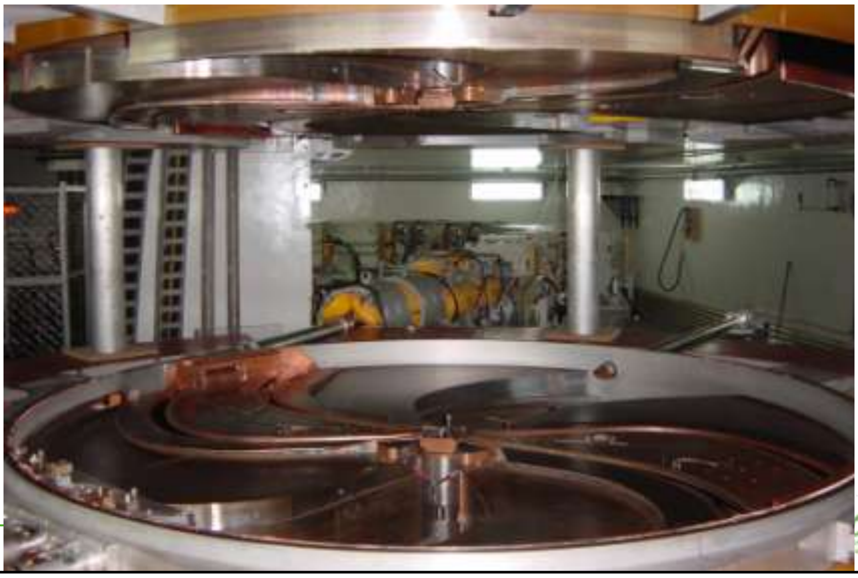
The 230MeV cyclotron opens in the median plane for service.

IBA PT subsystems : the Cyclone 235

Inside the accelerator

IBA PT subsystems : the Cyclone 235

Another view from the inside…



IBA PT subsystems : the Cyclone 235

The ion source and central region.

IBA PT subsystems : the beam transport lines.

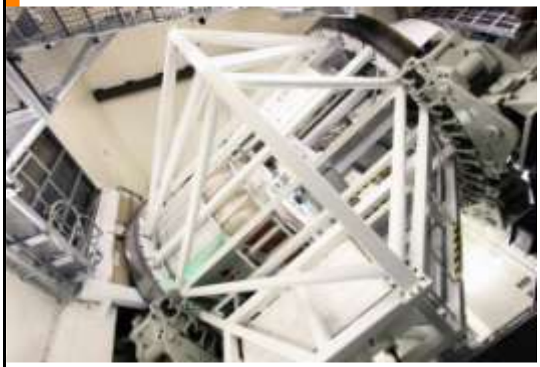
The energy selection system. Wanjie, China, 2003.

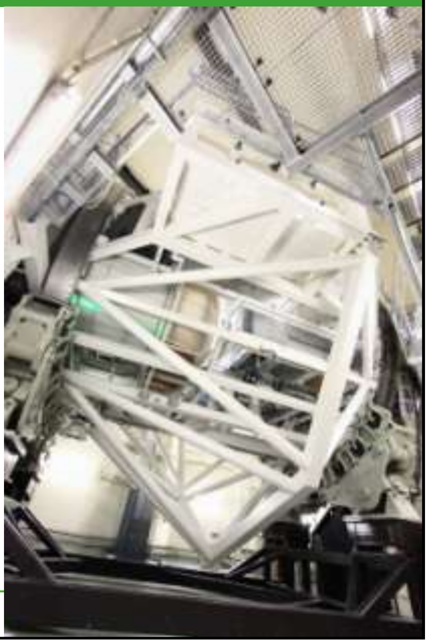
IBA PT subsystems : the beam transport lines.

The energy selection system. WPE, Essen, 2010.

IBA PT subsystems : the treatment rooms.

The isocentric gantry.





Carbon beam therapy

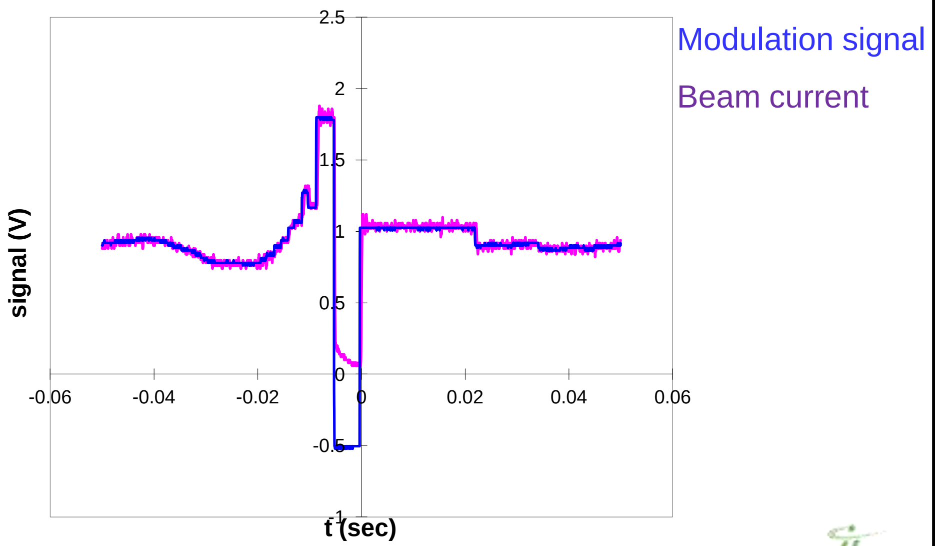
Why carbon beam?

- If protons are so good, why do you need carbon beams?
- Because some tumors do not respond to usual type of radiations: they are radioresistant. Ions heavier than protons are effective to treat such tumors

Cyclotrons for Proton & Carbon therapy?

- In 1991, when IBA entered in PT, the consensus was that the best accelerator for PT was a synchrotron
- IBA introduced a very effective cyclotron design, and today the majority of PT centers use the cyclotron technology (Not only IBA but Accel/Varian, Still Rivers Systems/Mevion)
- Over these 15 years, users came to appreciate the advantages of cyclotrons:
  - Simplicity & reliability
  - Intense, continuous (non pulsed) beam current
  - Lowest cost and size
  - But, most importantly, the ability to modulate rapidly and accurately the proton beam current

Real oscilloscope measured signals



Why is fast current modulation important?

- A big issue with scanned beam is the motion of the target during irradiation
- If you cannot control accurately and rapidly the current (synchrotron), or if the beam is pulsed (linac, FFAG), your only choice is step-and-shoot (spot scanning)
- Assuming a 10 mm (FWHM) beam spot size, a 50% overlap and a 20 Hz pulse rate, the maximum scanning speed will be 0.2 m/sec
- With this speed, for a large size tumor, repainting many time each layer is not really an option
- In contrast, with a cyclotron you can scan at 20 m/sec and rescan many times each layer

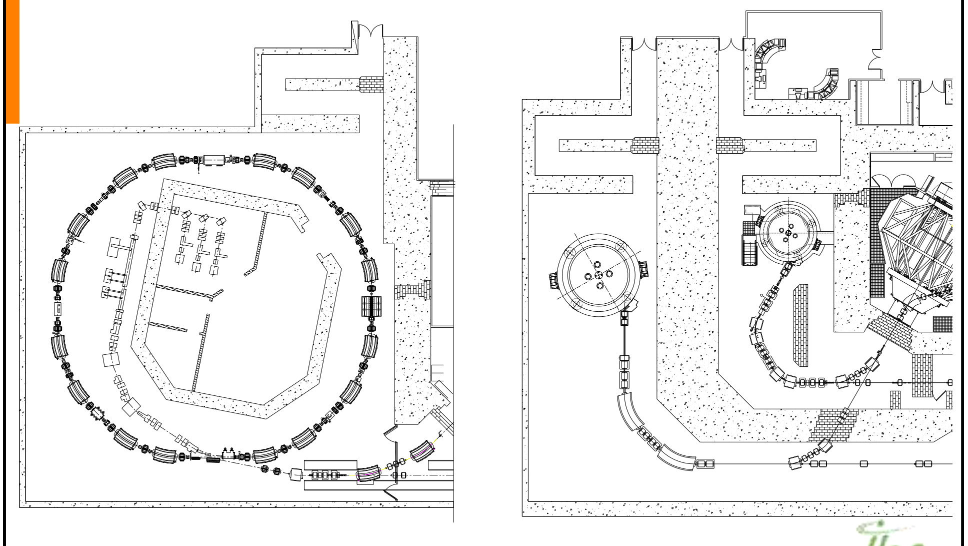
Change of energy?

- Cyclotrons are simpler at fixed energy
- Energy change by graphite degrader at waist after cyclotron exit, followed by divergence slits and energy analyzer
- This very effectively decouples the accelerator from the patient
- Fragmentation products are effectively eliminated in slits and ESS
- Yes, neutrons are produced, but ESS is well shielded and the average beam current in PT or CT is very low > little activation
- How fast? 5 mm step in energy in 100 msec at PSI (vs. 5 msec for Cyclinac). But respiration cycle is 2…4 seconds, so 100 msec is fine

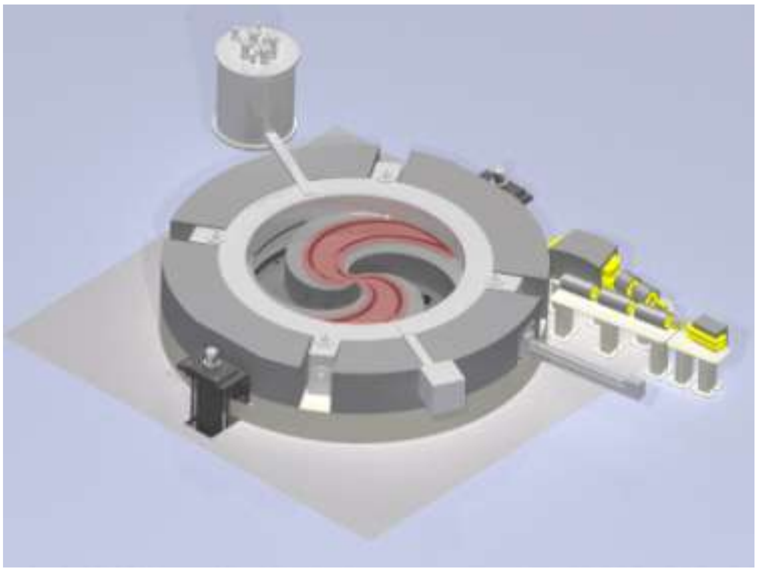
Simplicity and reliability

- A cyclotron for carbon therapy is a simple and relatively inexpensive machine
- In contrast, a synchrotron is a system of 2 (3?) accelerators in series.
- Fixed field, fixed frequency, no trim coils (isochronism obtained by iron shimming), main coil current linked to iron temperature.
- Simple RF: 2 dees, two 80 kW RF sources at fixed frequency
- 2 ECR sources + 1 multicusp source under the cyclotron with axial injection

In less space and cost than a synchrotron: a two cyclotrons phased approach



The C400 superconducting Carbon H2+ cyclotron



The IBA Carbon cyclotron design

- Superconducting isochronous cyclotron, accelerating Q/M = 1/2 ions to 400 MeV/U (H2 + (up to 250 MeV/u), Alphas, Li6 3+, B10 5+, C12 6+, N14 7+, 016 8+, Ne20 10+)
- Design very similar to IBA PT cyclotron, but with higher magnetic field thanks to superconducting coils, and increased diameter (6.3 m vs. 4.7 m)

Main cyclotron parameters

- Accelerated beam: 750 µA of H2+ up to 700 MeV
- Extraction by stripping of the H2+ into protons
- K bending 1600
- R extr.187 cm, Hill field 4.5T, Valley field 2.45T, weight 650t
- Design similar to IBA C400, with the following modifications:
  - Enlarged magnet gap at large radii
  - Higher power, 350 kW RF FPA for each cavity
  - Larger vacuum pumps
  - Protection and cooling of the central region

Extraction trajectories

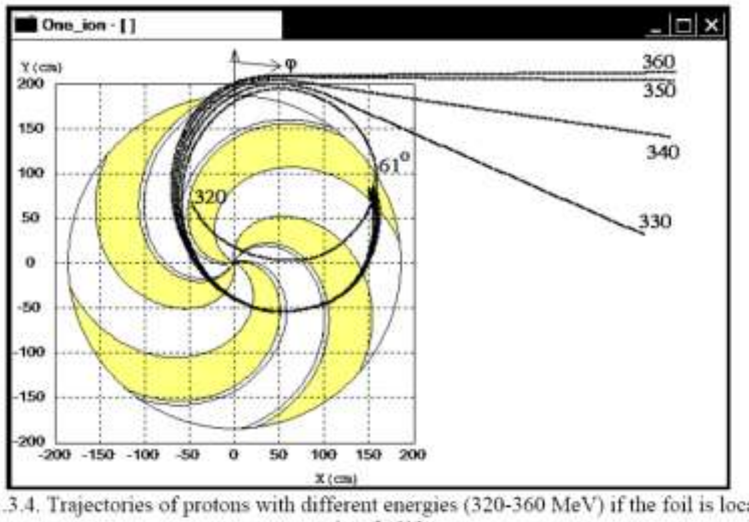


Fig. 6.1.3.4. Trajectories of protons with different energies (320-360 MeV) if the foil is located at azimuth 61°

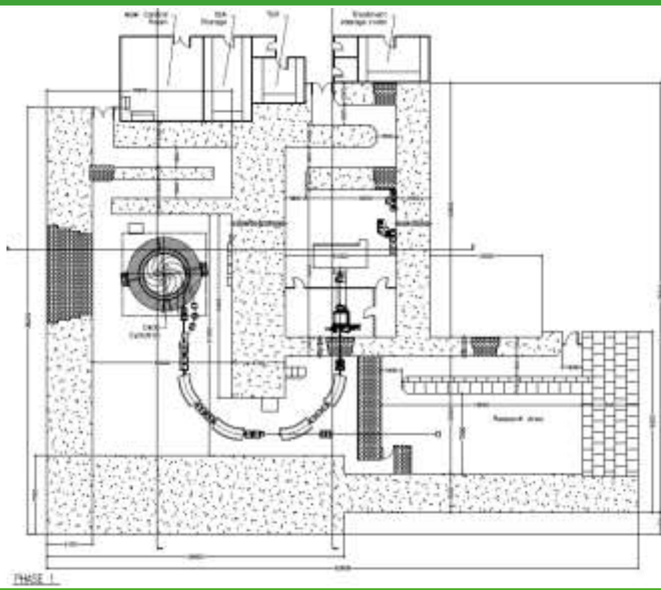
Status of the cyclotron in 2010

- During the last three years, a team of accelerator physicists at the JINR in Dubna has completed the physical design of the cyclotron.
- This study has been summarized into a comprehensive design report.
- In January 2007 and in April 2009 international design reviews were organized by IBA, with worlds key superconducting cyclotron experts.
- The outcome of the reviews were completely positive, and many inputs of the reviewers were included in the design.
- A design contest has been organized between the SC coils suppliers. The French company Sigmaphi was selected.

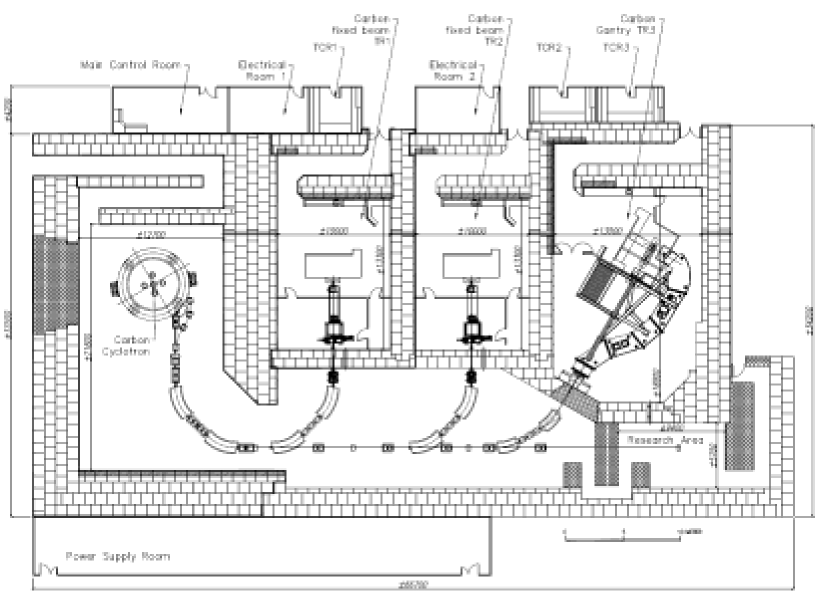
The proposed agreement with Archade (Caen)

- IBA will install the C400 prototype in Caen, close to the GANIL laboratory, within the frame of a research project with ARCHADE.
- The goal is to establish a center of resources and knowledge in hadron therapy, and to validate the IBA system
- The goal is not to create a clinical therapy center (Lyon's Etoile project comes first)

Archade project



A simple carbon therapy facility



Super Conducting Synchro Cyclotron

Why ?

- **Replace the existing C230 with a cheaper proton source.**
  - Reduced cash flow.
  - Reduced cost.
  - Reduced time to install.
  - Reduced full cost of acquisition.
- **This cheaper and smaller proton source will be part of a smaller and cost effective protontherapy system.**
- **PT "wish list" summed up in 4 numbers.**
  - 24 months from GO to Shipment.
  - 12 months for recurrent units.
  - 1 month from end of rigging to beam on degrader.
  - 5 treatment modes.

How ?

- **Reducing the size.**
  - Direct impact on weight thus costs.
  - Requires increasing the average magnetic field.
    - Magnetic field increase is incompatible with conventional magnets → Super Conducting magnet.
    - Magnetic field increase is incompatible with isochronous cyclotrons → Synchrocyclotron.
- **Reducing the complexity.**
  - Direct impact on costs, assembly and testing time.
- **Main impact on existing treatment modes.**
  - Beam time structure is pulsed instead of continuous.
    - Impacts dosimetry.
    - Impacts scanning controller.

How a Synchrocyclotron differs from a Cyclotron

Isochronous cyclotron:

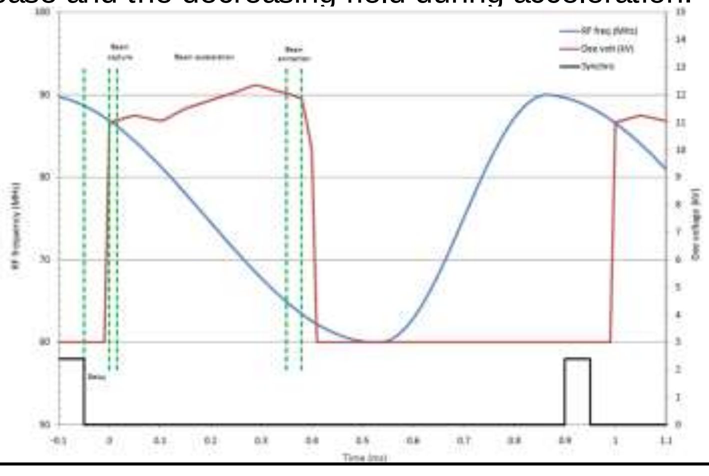
- Requires B to increase proportionally to m.
- Requires sector focusing for vertical stability.
- This leads to a smaller average magnetic field, thus a larger structure.
- All parameters being constant, operation is CW.

Synchro cyclotron:

- Requires B to decrease for weak focusing.
- Requires f to decrease during acceleration.
- Smaller structure due to high average magnetic field.
- Acceleration being frequency dependant, operation is pulsed.

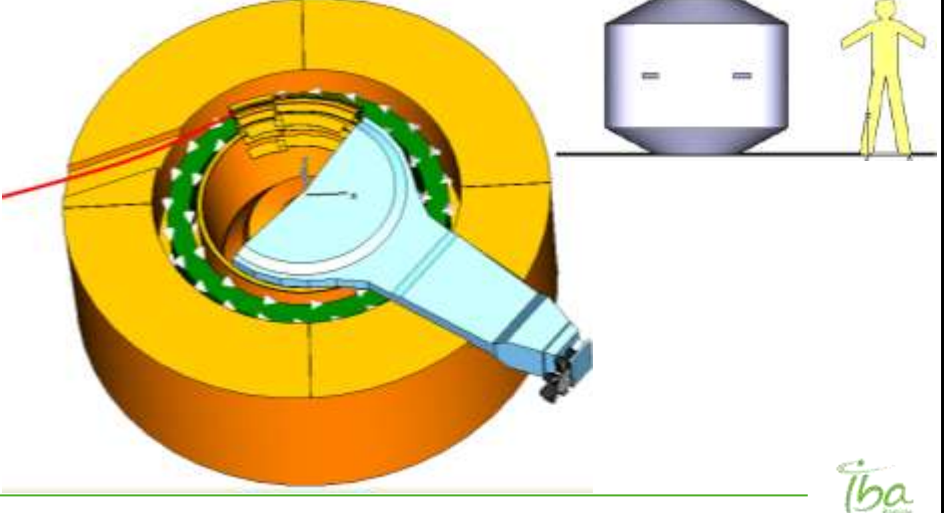
What is a Synchrocyclotron ?

A Synchrocyclotron is a circular accelerator in which the frequency of the accelerating electric field is modulated in order to compensate the decreasing period of revolution of the particles. This decrease is due to the relativistic mass increase and the decreasing field during acceleration.



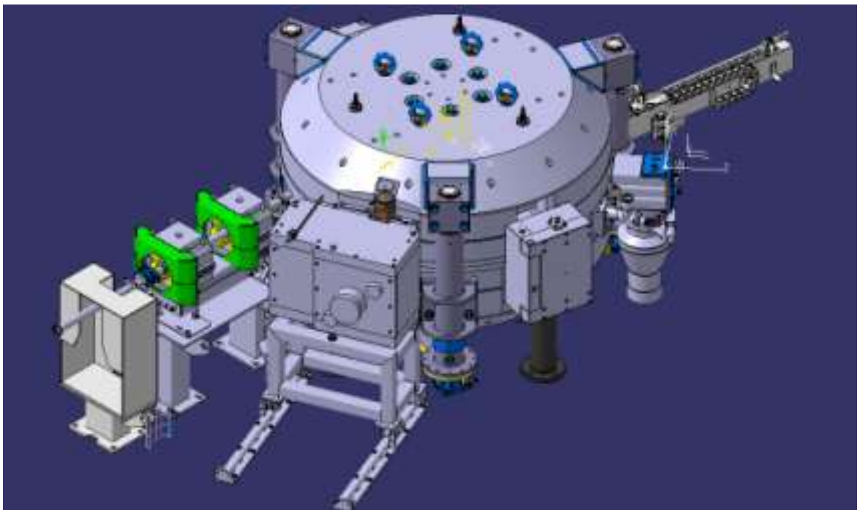
From concept…

The concept, as imagined back in 2009.



…to project

…and now, state of the project early 2013.



Specifications

- Compact system: dia.2.5m, height 2m, weight <50T.
- Reliability: NbTi cryogen free coil, passive extraction…
- 1kHz beam pulse repetition rate for PBS.
- 20nA, 230MeV for PBS.
- Still possible to reach 250MeV and 150nA with some additional work if required.

Why is it challenging ?

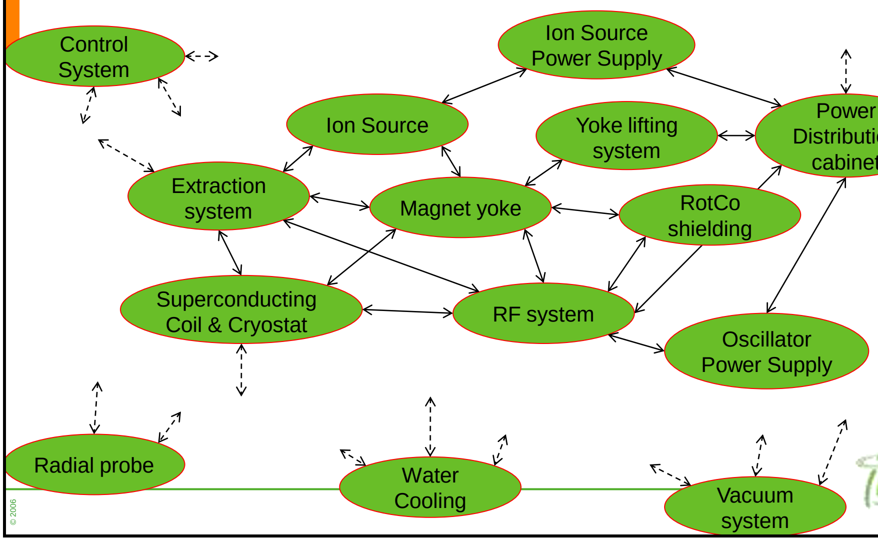
- **Super conducting coils.**
  - Well known and documented technology but never used in IBA products so far (Cryostat, quench protection, control…).
- **High magnetic field cyclotrons.**
  - Introduces complexity in the injection and extraction system (small size of central region, stray field…).
- **RotCo modulated HF.**
  - Critical mechanical structure that has never been used in IBA products so far (in vacuum fast rotating water cooled mechanical structure with tight tolerances).

Why is it challenging ?

- **Resonant extraction.**
  - Field bump to excite a first harmonic to separate turns in order to extract through a magnetic channel has never been used on IBA products (regenerator, magnetic channel…).
- **Synchrocyclotron.**
  - Longitudinal beam dynamic is very different from isochronous cyclotrons (beam capture, phase stability, energy distribution…).
- **Industry pressure.**
  - Extremely short schedule from concept to prototype.
  - Designed to be operator less.
  - System uptime should be greater than 99%.

More challenging than expected ?

A major difficulty lies in the close interdependance of all sub-systems, leading to frequent cascaded redesign.



Isochronous vs synchro cyclotron

C230 isochronous cyclotron

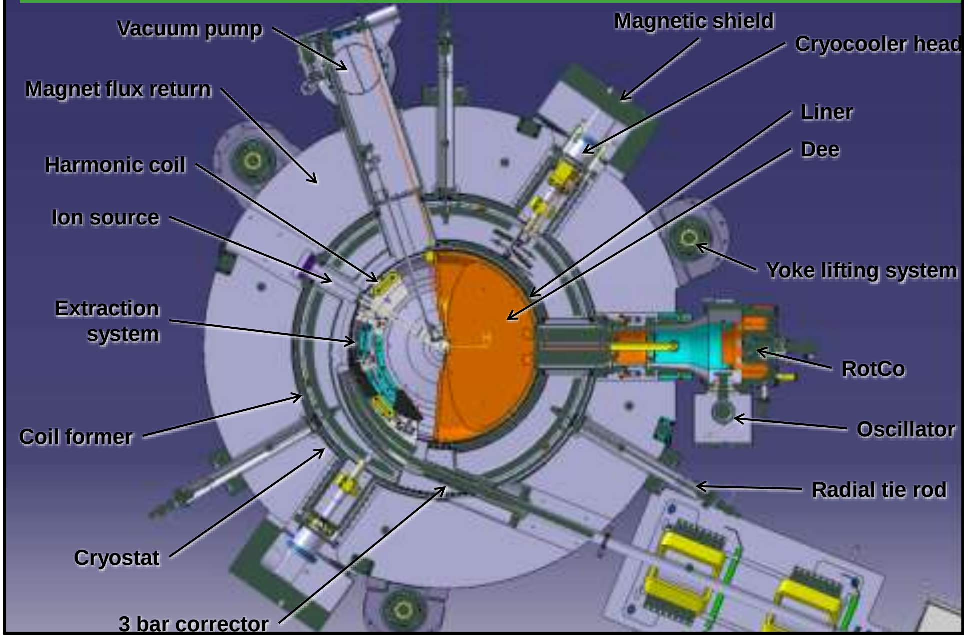
- Diameter: 4.34m
- Weight: 210 tons
- Conventional magnets
- *Bavg*: 1.74T to 2.2T
- Dee voltage: 55kV to 150kV peak
- Rf frequency: 106MHz
- Quasi continuous beam
- Average beam current: 300nA
- Energy: 230MeV (0.6MeV @2σ)

S2C2 synchrocyclotron

- Diameter: 2.30m
- Weight: <50 tons
- Superconducting magnets
- *Bavg*: 5.64T to 5.24T
- Dee voltage: 14kV peak
- Rf frequency: 90MHz to 60MHz
- Pulsed beam at 1kHz rep rate
- Average beam current: 150nA
- Energy: 230MeV (2.5MeV @2σ)

Capable of running at 250MeV if required with magnetic field and rf frequency increased by 4%

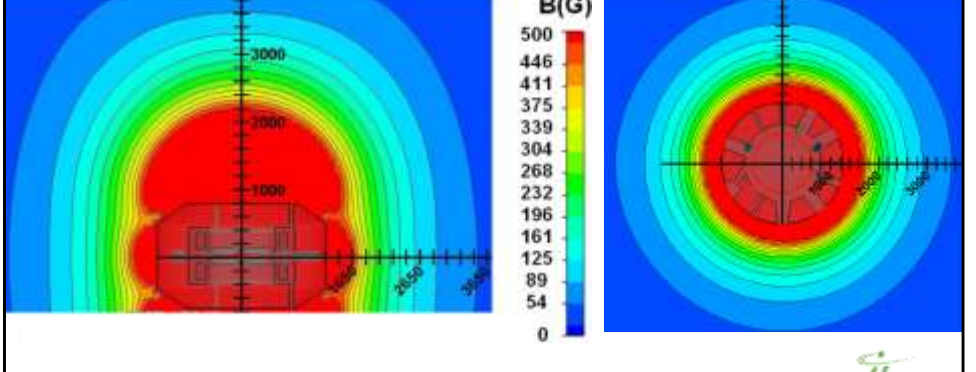
Super Conducting Synchro Cyclotron



Magnet Yoke

The yoke size is a delicate compromise between coil complexity, peak field, stray field and total weight.

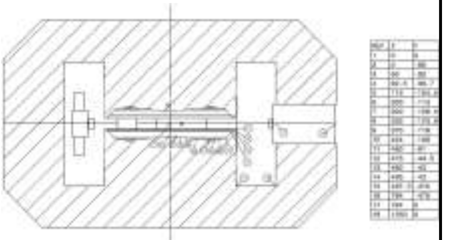
Also, it allows to stay away from any SRS or MIT patents and use cheap and readily available NbTi.

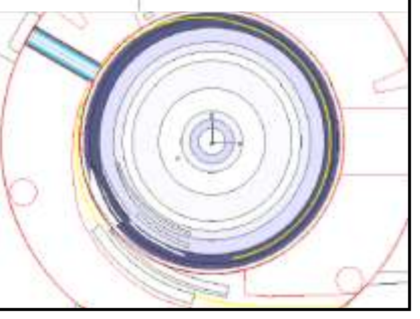


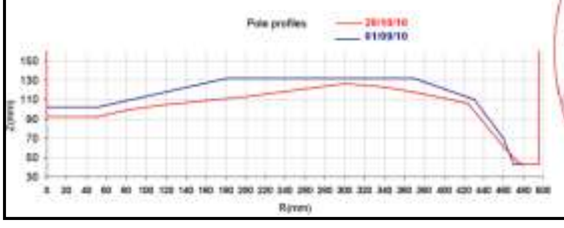
Magnet Yoke

The pole profile is the result of an optimized extraction system:

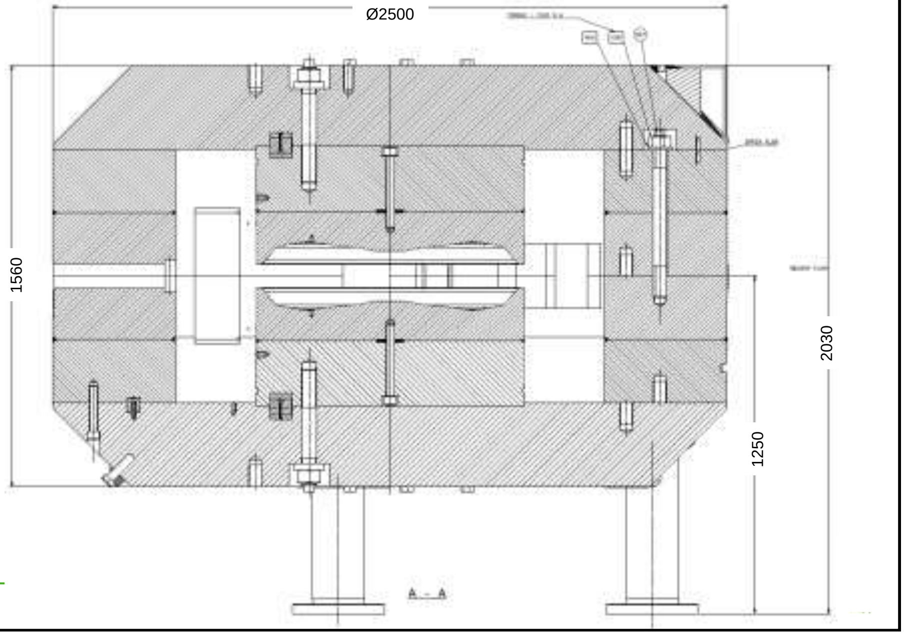
- higher vertical focusing before extraction: less vertical losses during regeneration process.
- faster dropping field after regeneration, making the extraction more efficient for a given azimutal length through the cryostat.



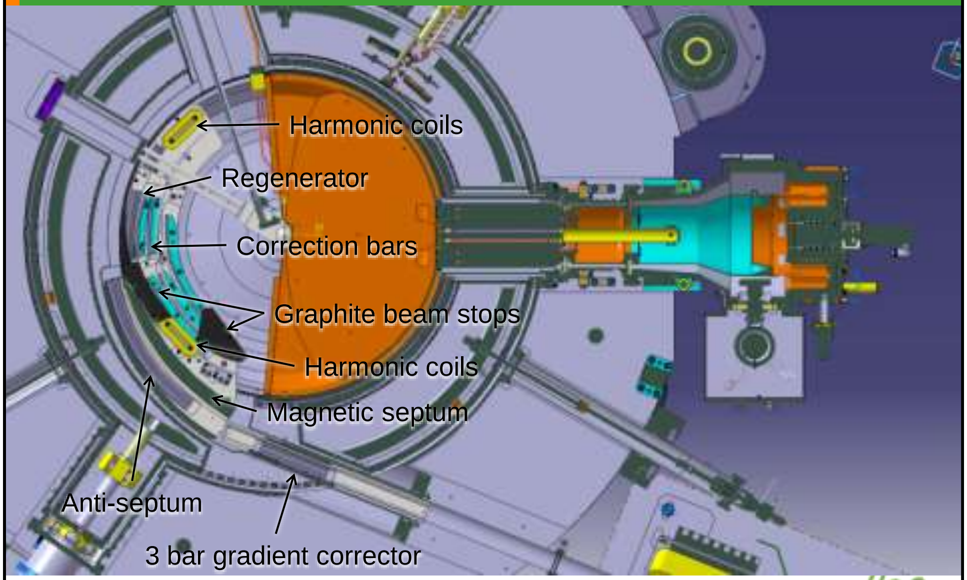




Magnet Yoke



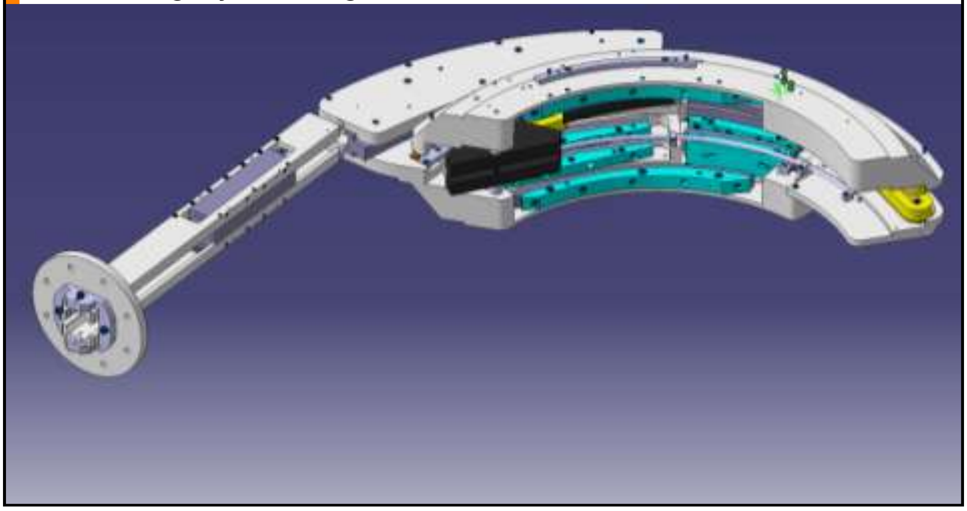
Extraction System



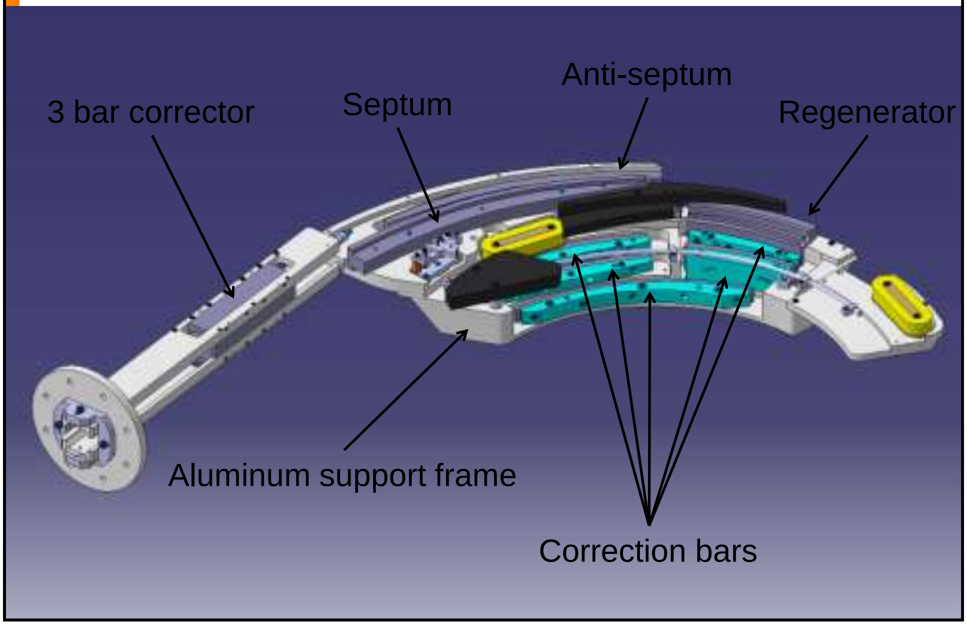
Extraction System

Extraction system is completely passive.

It is composed of iron bars on stainless steel supports, all of them rigidly held together on an aluminum frame.

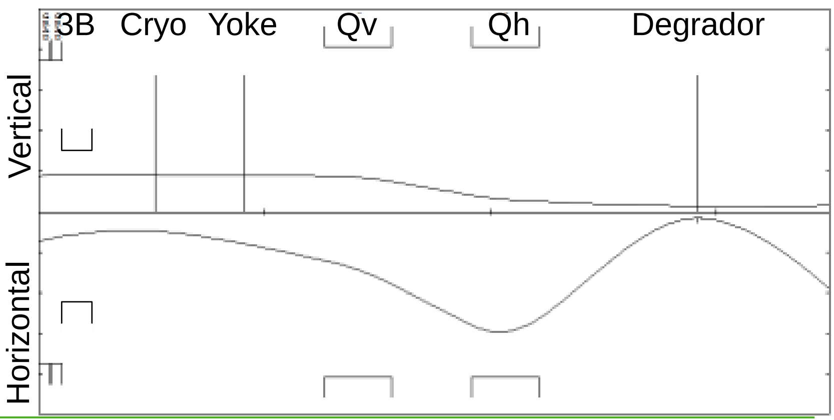


Extraction System



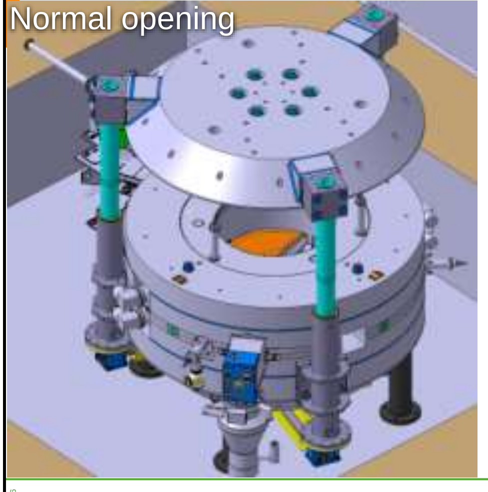
Extraction System

Optical solution found using a passive three bar corrector in the cryostat beam exit tube and a active quadrupole doublet between yoke and degrador.



Yoke Lifting System

The yoke lifting system offers also the possibility to open at the median plane as well as above the return yoke.



Cryostat

NbTi coil

Conduction cooled

230MeV:

647A, 55.6A/mm²

9.37MJ

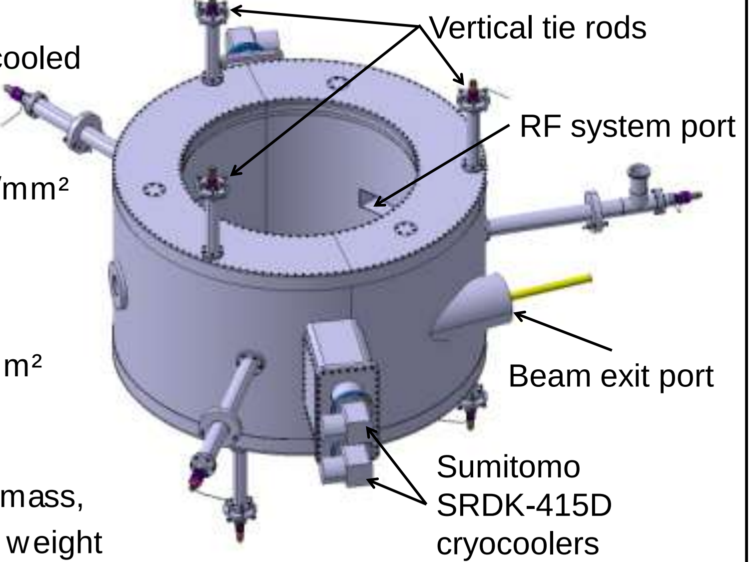
250MeV:

691A, 59A/mm²

10.60MJ

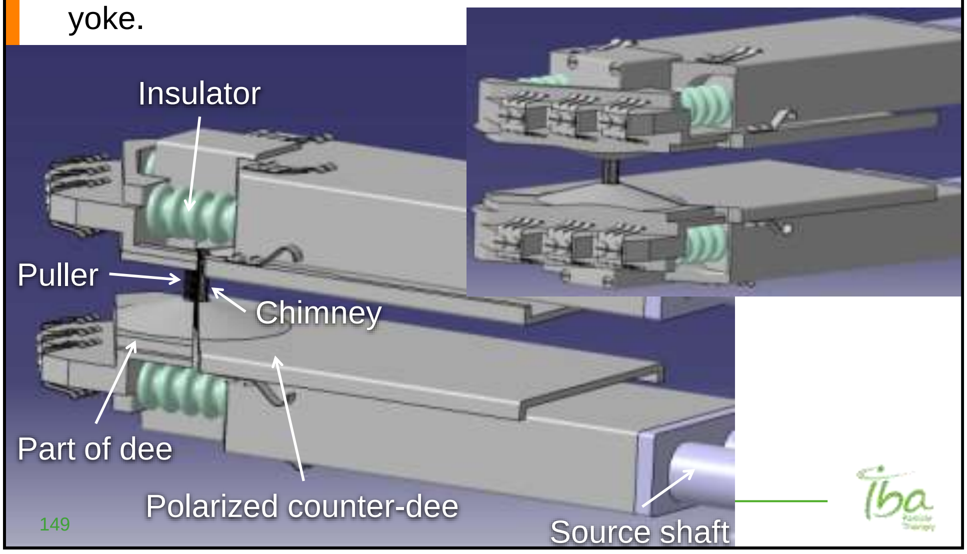
3.1tons cold mass,

4tons overall weight



Ion Source

The Ion Source assembly, including the central region, can be extracted for maintenance without having to open the magnet yoke.



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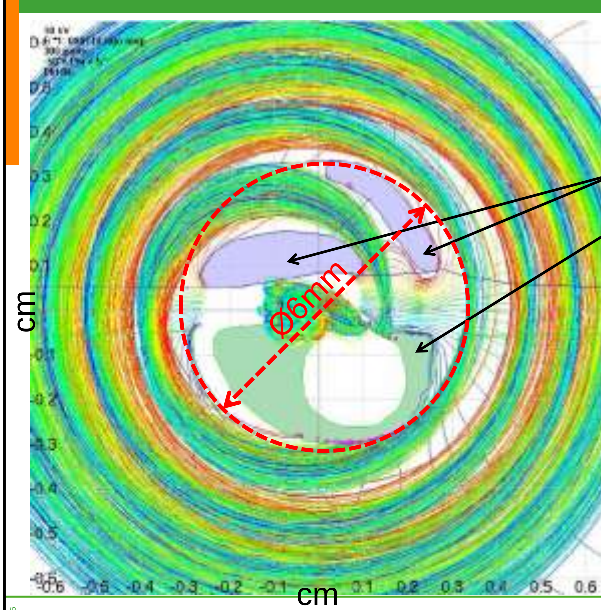
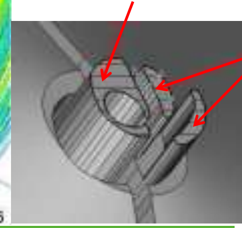
Central region



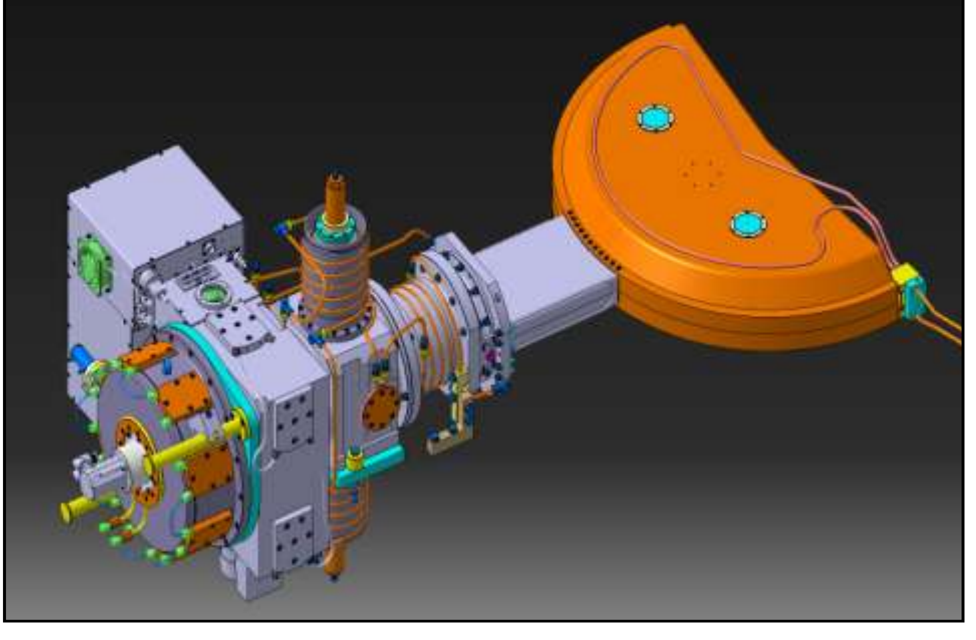
It has to be extremely small !



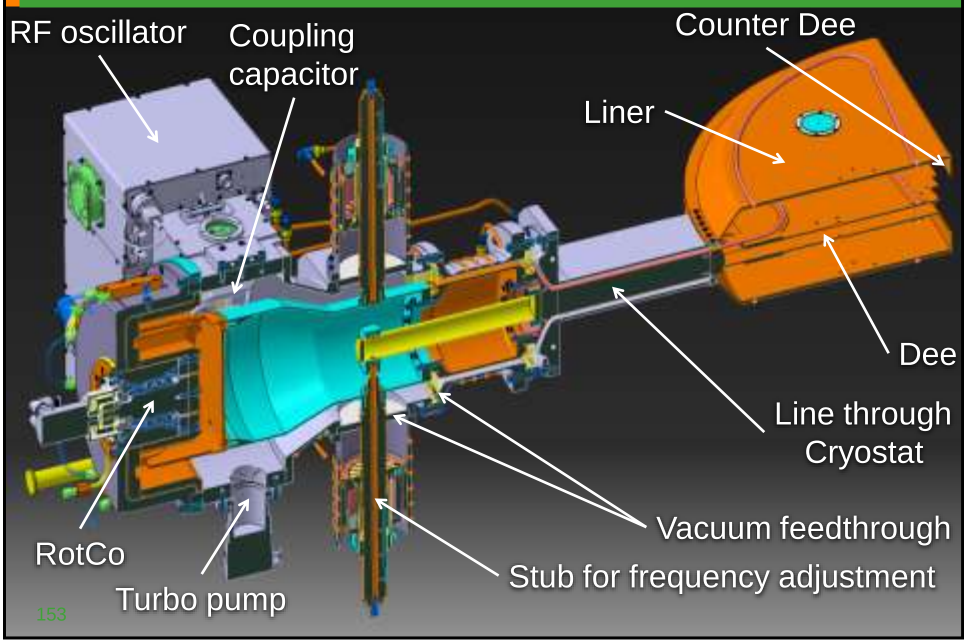
Central region

151

RF system

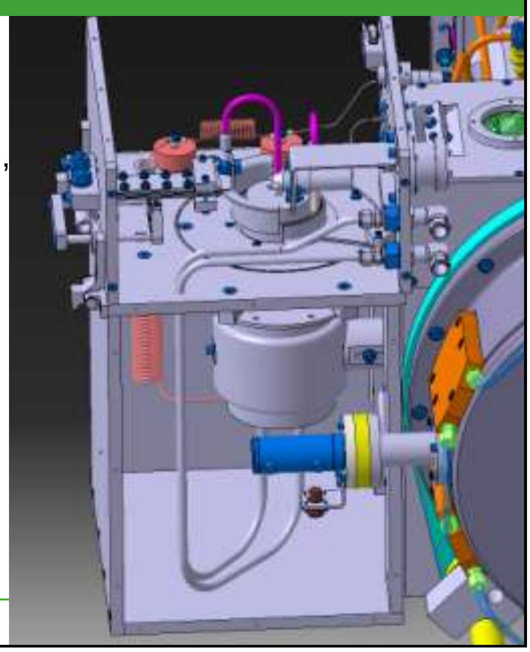


RF system



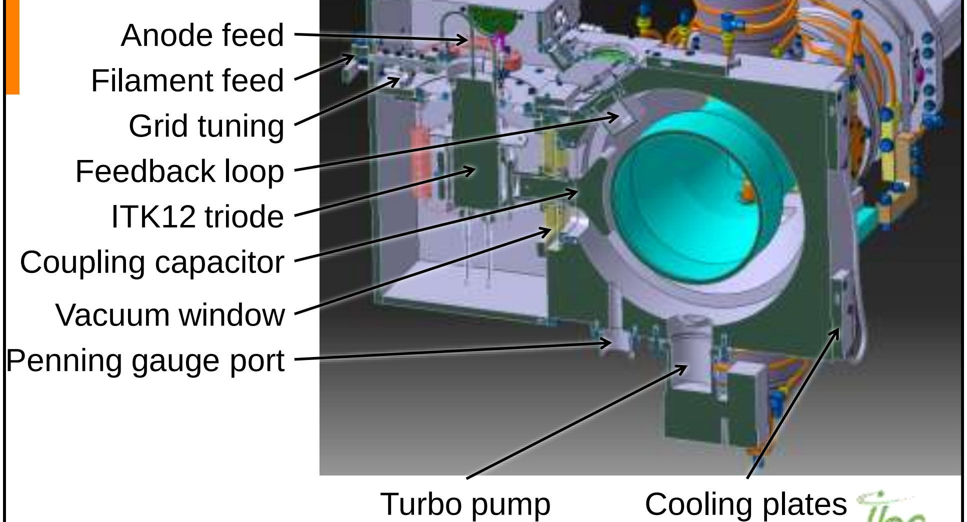
RF system

Hartley type oscillator driving the RF structure at its own resonant frequency. Build around a Thales ITK12 triode, connected in grounded grid mode and a cathode reinjection in phase supplied by an adjustable voltage pick-up loop in the main resonator. It starts oscillating as soon as the anode voltage is applied. The anode is coupled to the stem through an adjustable capacitor.



RF system

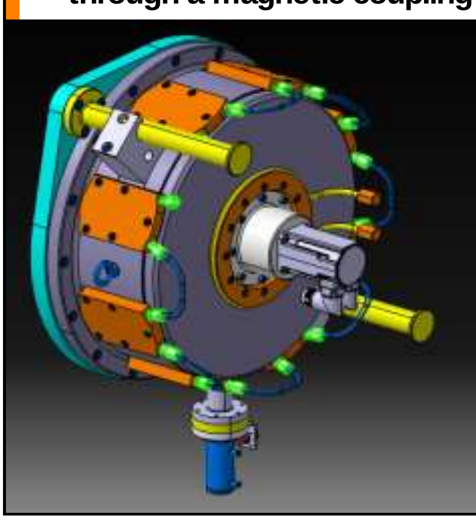
Oscillator

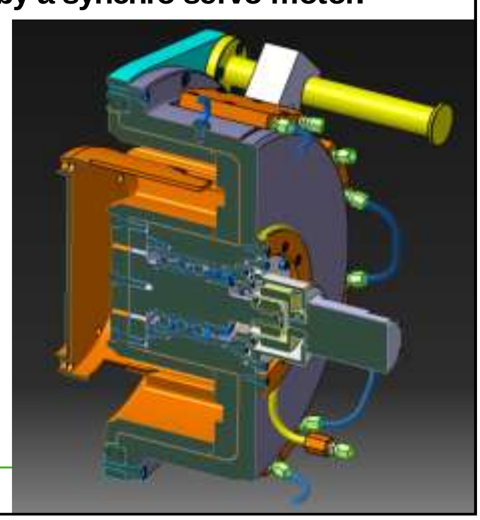


RF system

RotCo

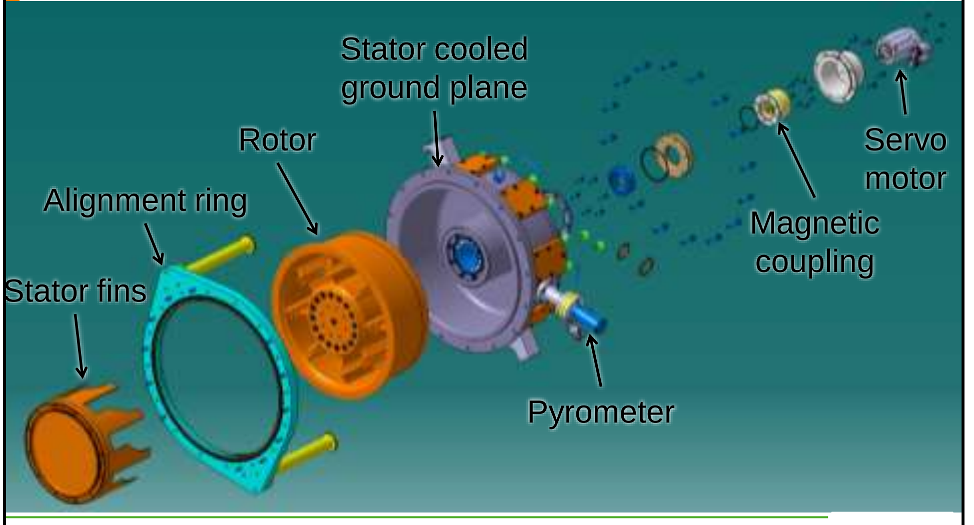
8 blades rotating at 7500rpm, on hybrid bearings, driven through a magnetic coupling by a synchro servo motor.





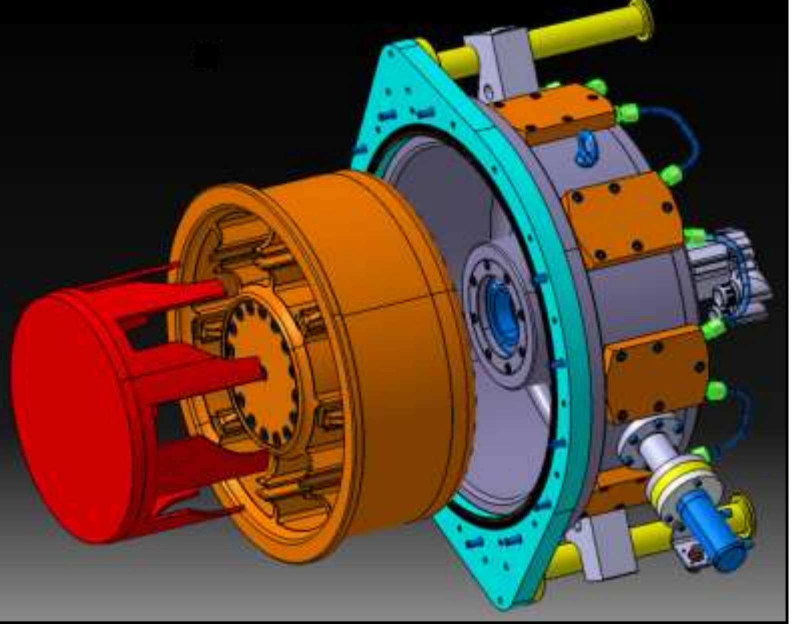
RF system

RotCo



RF system

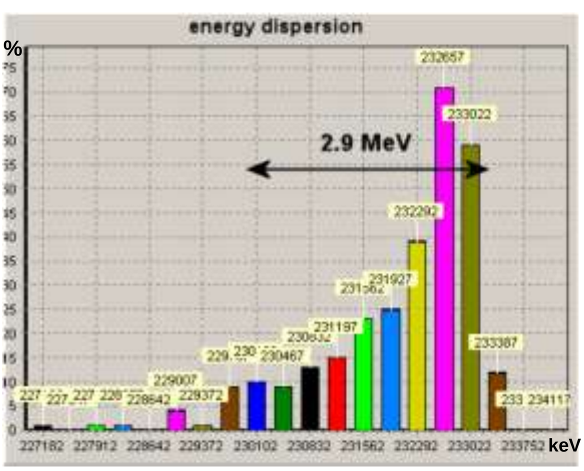
RotCo



RF system

Beam structure

Energy distribution:



Impact of an « operator less » system

Hardware

- Increase the intrinsic reliability by design.
- Reduce the failure risk of routine operations.
- Redundancy: spare parts are build-in, online and ready to operate without human intervention instead of spare parts waiting on a shelf.
- Standardization: reduction of number of different items whenever possible to reduce RSPL and MTTR.
- Diagnostics: add transducers to monitor equipment.
- Reduce the tooling required to maintain the system.

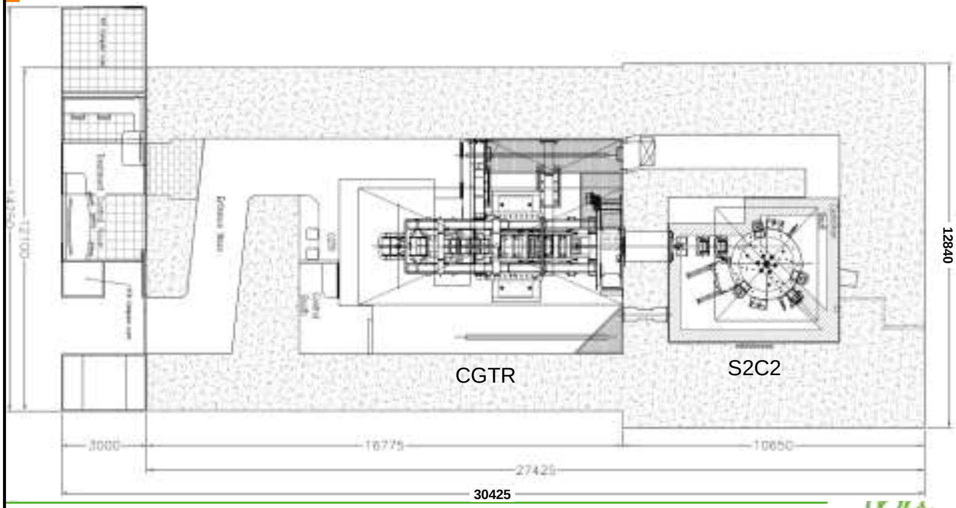
Impact of an « operator less » system

Software

- Single button full automatic startup with morning check.
- Implement different modes of operation: normal and degraded.
  - Degraded mode allows to proceed with patient treatment while HMI gives a clear warning message.
- Robust historian and extensive remote diagnostics.
- HMI gives clear instructions allowing staff to schedule the next maintenance.

Proteus One®

Small footprint: 30.5m x 13.0m



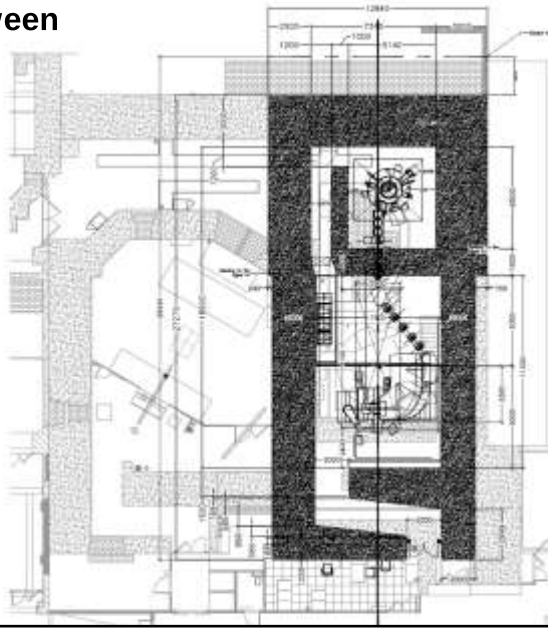
Proteus One vs Proteus 235 Layout

Comparison between

Proteus 235:
C230 + GTR

&

Proteus One:
S2C2 + CGTR



Proteus One®

Industrial applications

Defining Industrial Applications of Accelerators?

- Generally, high energy particle beams induce nuclear reactions and activation
- In contrast, in industrial applications, nuclear reactions and activation are undesirable and avoided, but other effects of ionizing radiations are researched
- These desired effects include:
  - Sterilization
  - Cross linking of polymers
  - Curing of composite materials
  - Modification of crystals
  - Doping of semi conductors
  - Beam aided chemical reactions
  - Thermal or mechanical effects of the particle beam

Which beams are used?

- The choice of particle beams used in industrial applications is defined, to a large extent, by the desire to avoid nuclear reactions and activation.
- Commonly used beams include:
  - Electron beams below 10MeV.
  - X-Rays from e-beams below 7.5MeV.
  - Intense, low energy proton beams.
  - Heavy ion beams well below the Coulomb barrier.
- Also, for industrial applications, large beam currents/powers are needed to reach industrial scale production rates. Beam powers from 50 kW to 1 MW are common.

Key E-beam and X-ray Industrial Applications

- **Sterilization**
  - Sterilization of Medical Devices
  - Surface Sterilization
  - Food Pasteurization
- **E-beam induced chemistry**
  - Reticulation of Polymers
  - Curing of composites
  - Environment remediation
- **E-Beam induced crystal defects**
  - Modification of Semiconductors
  - Coloring of Gemstones

The options for the sterilization of medical devices

- Steam (incompatible with most polymers)
- Ethylene Oxyde
  - Inexpensive
  - EtO is explosive, toxic and harmful to the environment
  - EtO sterilization may leave harmful residues
- Irradiation
  - Cobalt
  - E-beam
  - X-ray

The options for sterilization by irradiation (1)

- **Gammas from Co60**
  - Low investment cost, specially for low capacities
  - Simple and reliable, scalable from 100 kCuries to 6 MCuries
  - Isotropic radiation > inefficiencies in use
  - Pallet irradiation, but low dose rate > slow process
  - Absolutely no activation
  - Cannot be turned OFF > inefficient if not used 24/7
  - Growing security concern: the cobalt from a sterilization plant could be used to make dirty bombs

The options for sterilization by irradiation (2)

- **Electron beams**
  - Directed radiation > Efficient use
  - Lowest cost of sterilization for large capacities
  - Can be turned OFF > safer
  - Short range (4.5 g/cm² at 10 MeV) > 2-sided irradiation of boxes
  - More complex dose mapping
  - Minimal, hardly measurable, but non zero activation

The options for sterilization by irradiation (3)

- **X-Rays from E-beams**
  - Excellent penetration
  - Simple dose mapping
  - Pallet irradiation
  - Directed radiation > Efficient use
  - Loss of a factor 10 in energy when converting e-beams to photons
  - Cost of sterilization higher than electrons
  - Cost of sterilization is generally higher by X-Rays than Cobalt if used 24/7, excepted for very large capacities
  - Can be turned OFF > safer
  - Minimal, hardly measurable, but non zero activation

Food irradiation applications

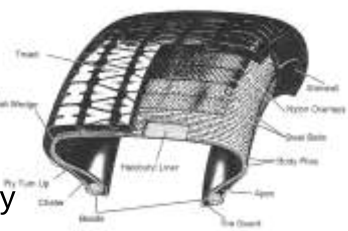
- **Low Dose Applications (< 1kGy)**
  - **Phytosanitary** Insect Disinfection for grains, papayas, mangoes, avocados...
  - **Sprouting Inhibition** for potatoes, onions, garlic...
  - **Delaying of Maturation**, parasite disinfection.

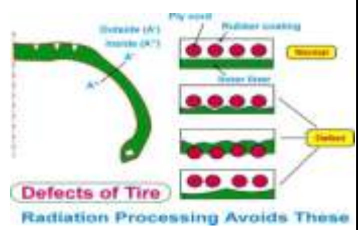
- **Medium Dose Applications (1 – 10 kGy)**
  - **Control of Foodborne Pathogens** for beef, eggs, flounder-crab-meat, oysters...
  - **Shelf-life Extension** for chicken and pork, low fat fish, strawberries, carrots, mushrooms, papayas...
  - **Spice Irradiation**

- **High Dose Applications (> 10 kGy)**
  - **Food sterilization** of meat, poultry and some seafood is typically required for hospitalized patients or astronauts.

E beam treatment of Tires

- Reduction in material hence in the weight of the tire
- Relatively low cost synthetic rubber can be used instead of costly natural rubber without a loss in strength
- The radiation pre-vulcanization of body ply is achieved by simply passing the body ply sheet under the scan horn of an electron accelerator to expose the sheet to high-energy electrons
- Higher production rates
- Construction of green tires
- Reduction of production defects



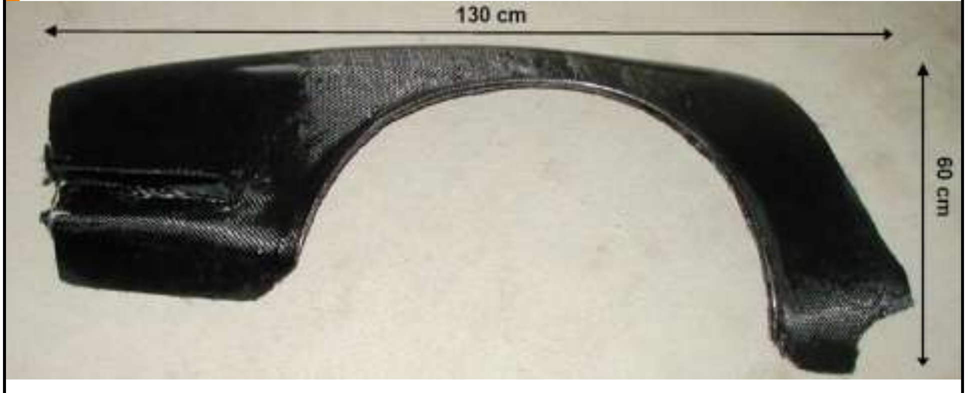


Polymer Cross-Linking

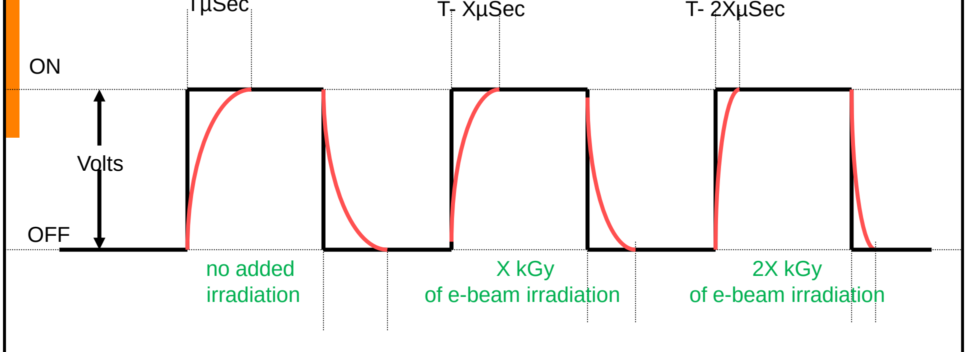
- **Wires** stand higher temperature after irradiation
- **Pipes** for central heating and plumbing
- **Heatshrink elastomers** are given a memory

Composite curing: X-ray Cured Carbon Fiber

- Sports Car Fender made light, restistant and requiring less fuel



E-beam irradiation improves SC switching speed

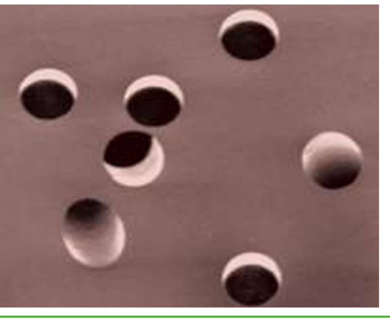


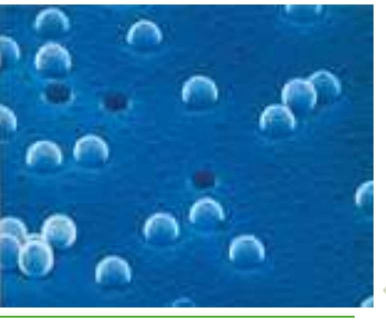
Typical semicondutors:

- fast recovery diodes
- power diodes
- Bipolar power transistors
- power MOSFETs
- power rectifiers
- IGBT's
- thyristors
- silicon-controlled rectifiers

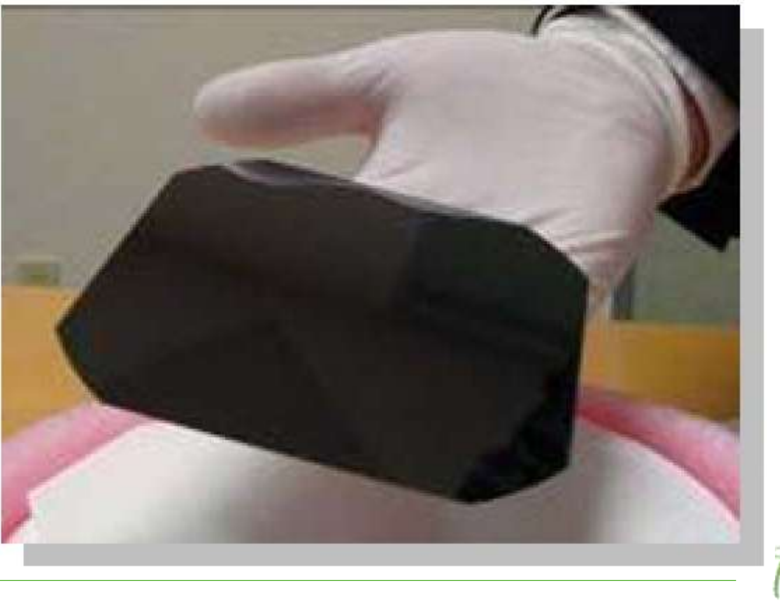
Microfiltration membranes by heavy ions

- Heavy ion beams are used to produce track-etched microfiltration membranes, commercialized i.a. under the brand name " Cyclopore"
- In these membranes, tracks of slow, heavy ions crossing a sheet of polymer are chemically etched, giving cylindrical pores of very accurate diameter

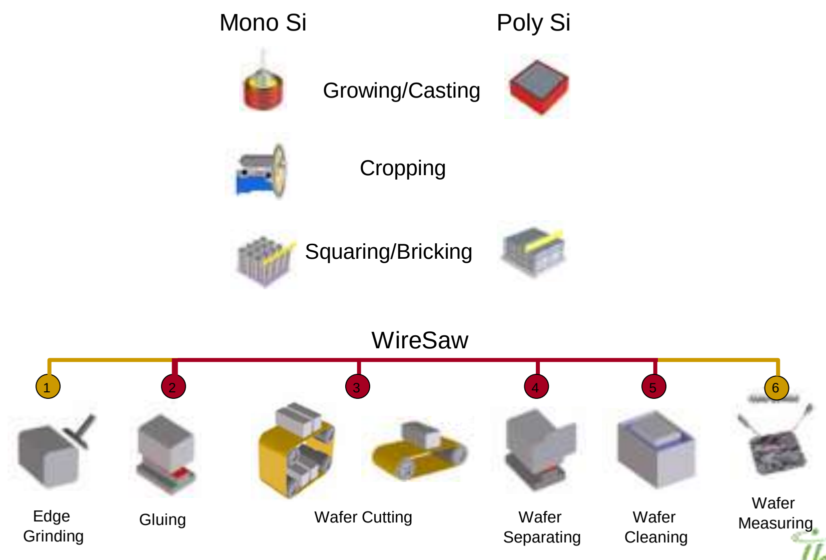




Industrial application of the Bragg Peak

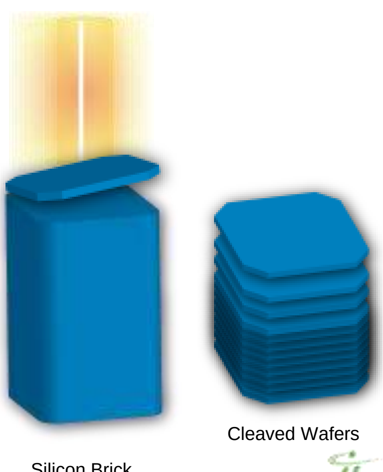


The present process using wire saws

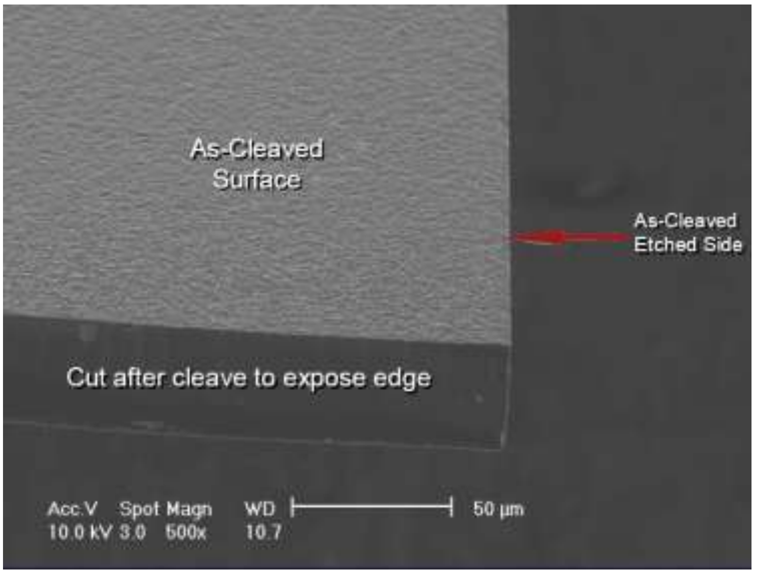


Sigen « Direct Cleave » AKA « Beam Saw » process

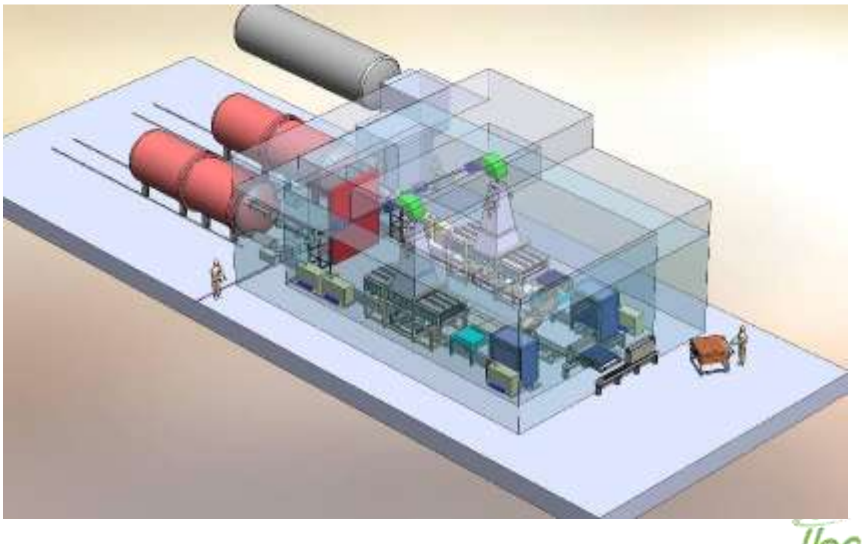
- Two Step Process
  - (1) Implant 2…4 MeV protons (20 mA)
  - (2) Cleave
- Eliminates Kerf Loss
- Eliminates Consumables
  - SiC, Slurry, Wire
- Eliminates Other Systems
  - Gluing
  - Singulation
  - Cleaning
  - Less Damage Etch



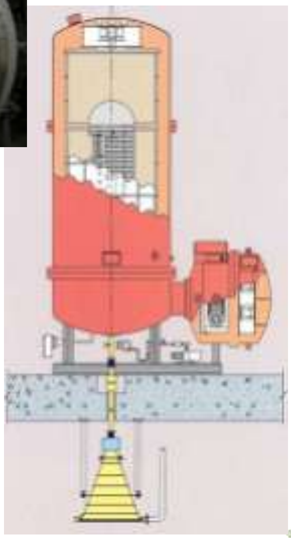
SEMS of the as-cleaved edge



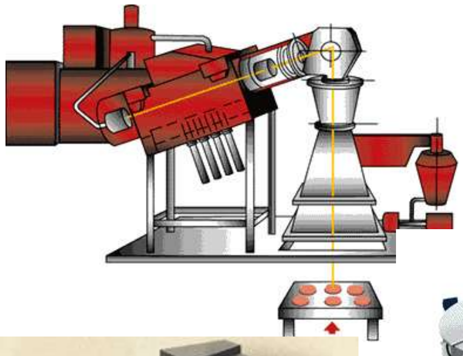
Industrial silicon cleaving equipment "Dynasolar"

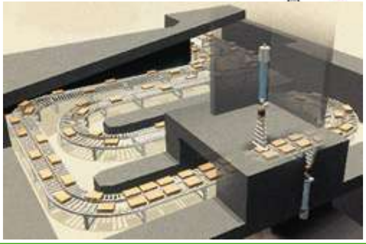


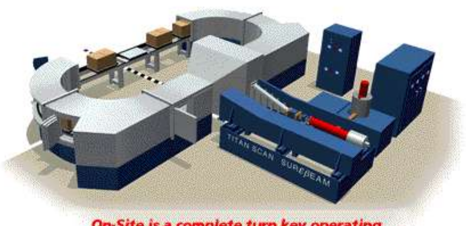
High power E-beam accelerators: 1) the Dynamitron



High power E-beam accelerators: 2) the Linacs



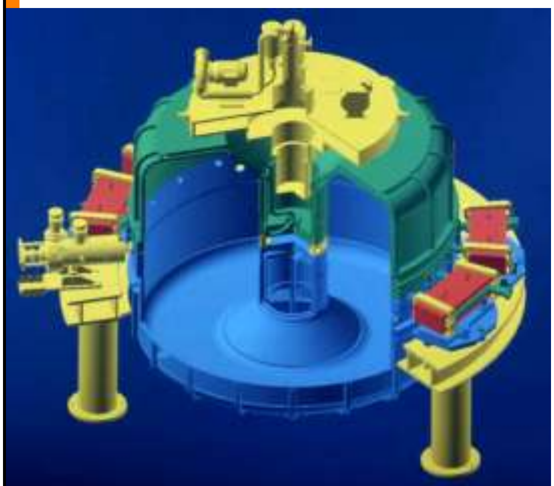




On-Site is a complete turn key operating system validated to ISO 11137 and delivered with all required training, documentation, dosimetry system and process certification.

High power E-beam accelerators: 3) the Rhodotron

- **Typical applications of the Rhodotron:**



- Modification of polymers
- Sterilization of medical devices
- Preservation of foods
- Treatment of waste materials
- Gemstones and semiconductors

Rhodotron

- **TT200 – TT300**

Rhodotron

- TT1000

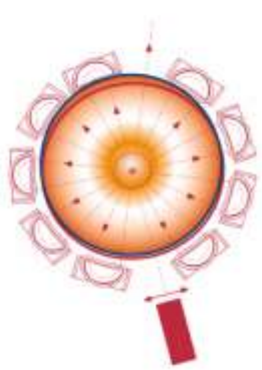
Rhodotron

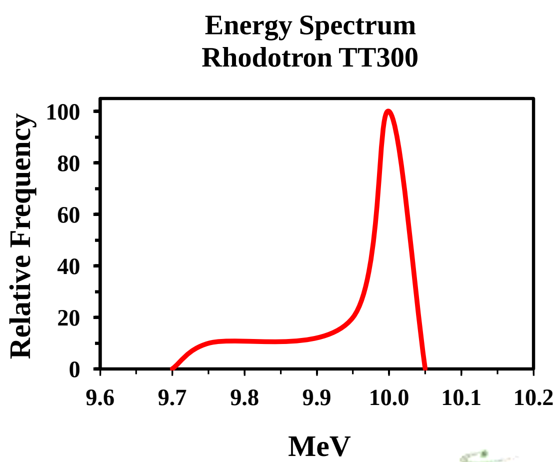
Rhodotron

	TT100	TT200	TT300	TT1000
Beam energy (MeV)	3~10	3~10	3~10	2.4~7
Maximum beam power (kW)	35	80	190	700
Design value (kW)	45	100	200	1000
Cavity diameter (m)	1.60	3.00	3.00	3.00
Cavity height (m)	1.75	2.40	2.40	2.40
Weight (T)	2.5	11	11	12
MeV/pass	0.833	1.0	1.0	1.167
Number of passes	12	10	10	6
Electrical power at full beam	<210	<260	<440	<1300

Rhodotron

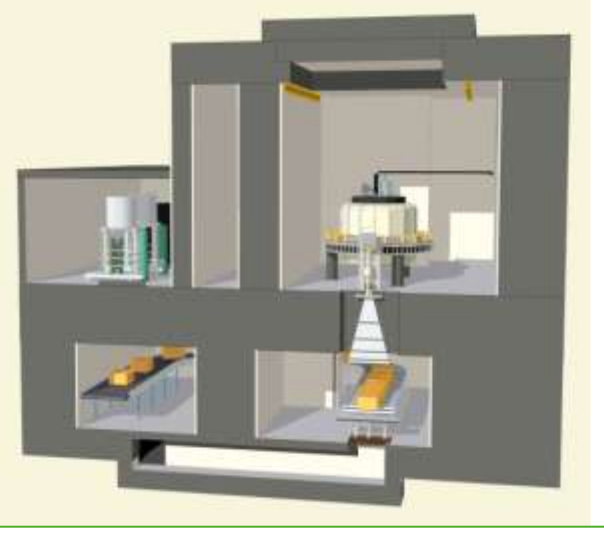
- **Multiple checks on beam energy**
  - Each magnet is a energy filter





Rhodotron

- Typical layout of an irradiation center

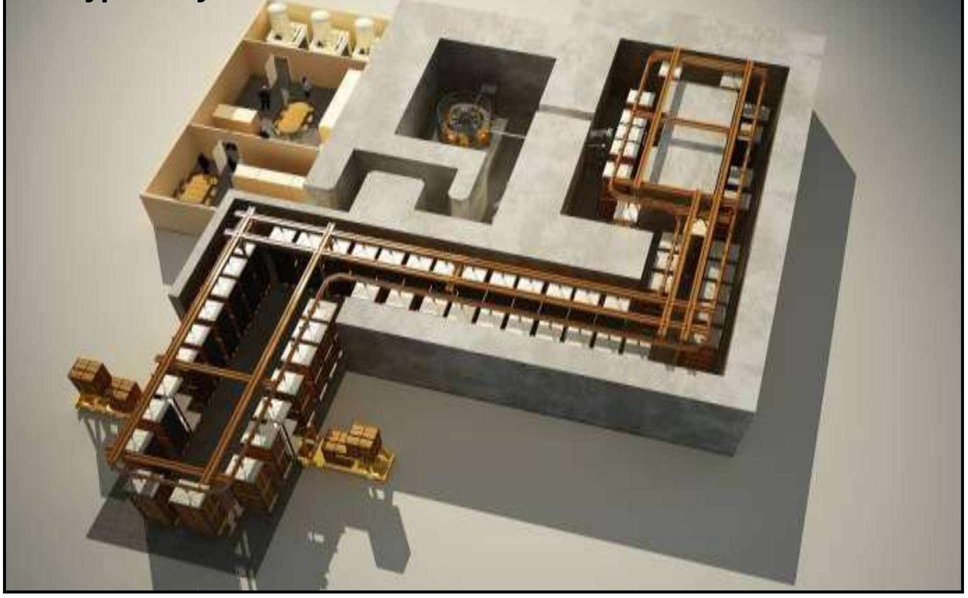


Rhodotron

- Typical layout of an irradiation center

Rhodotron

- Typical layout of an irradiation center



Thank you !

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