The medical applications of cyclotrons

CAS
Bruges, June 23 2009

Yves Jongen

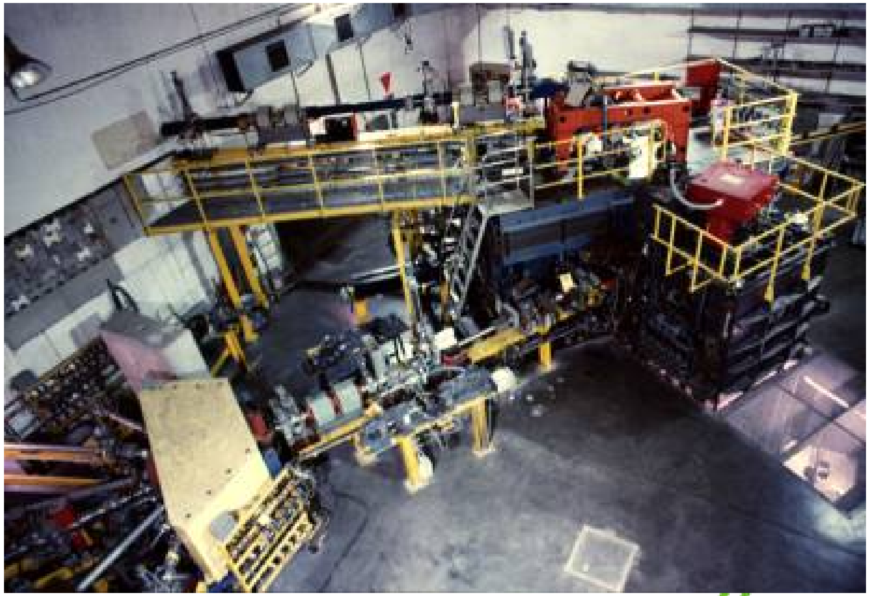
Organization of the lecture

- Introducing IBA
- Cyclotrons for the production of radioisotopes for medical diagnosis applications
- Proton therapy
- Carbon therapy

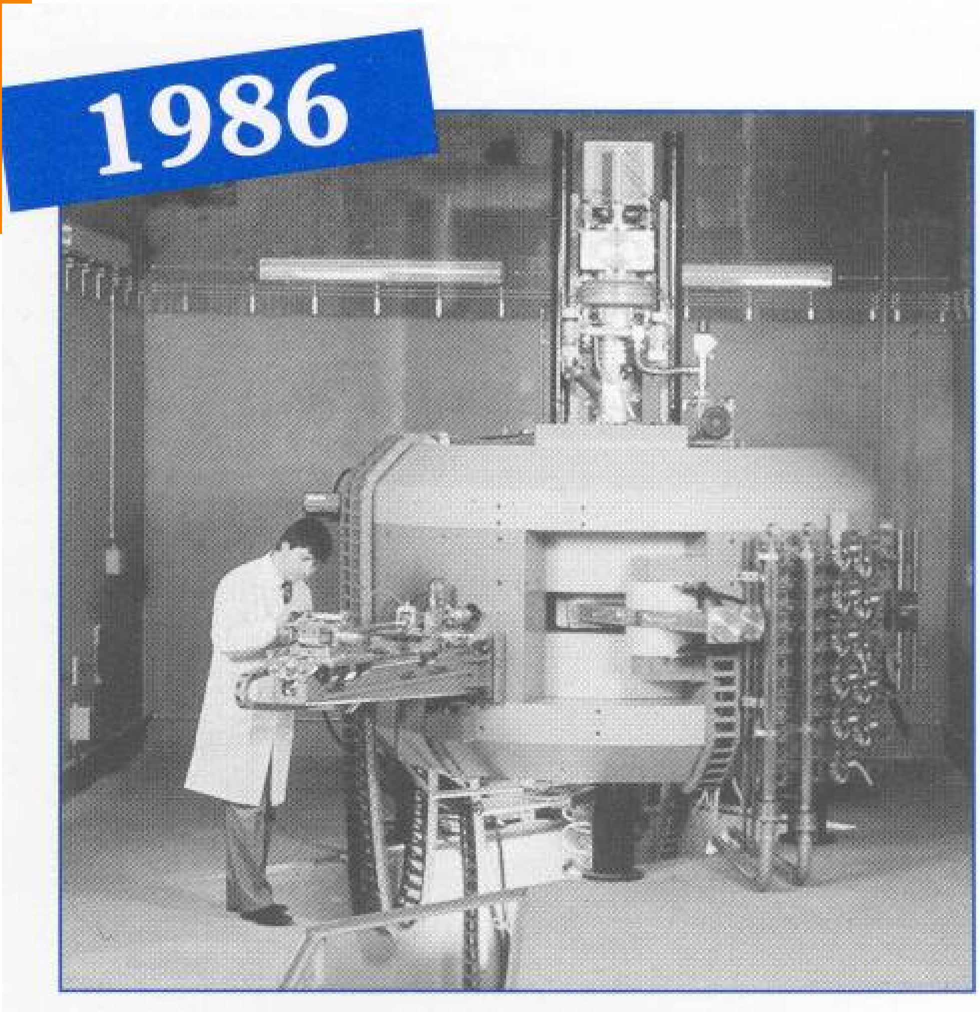
… an insult in Belgian cartoons?

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 our university team imagined to produce a cyclotron for the production of medical radioisotopes…
- Producing 5x more output and consuming 3x Less energy than any existing cyclotrons…
- Truly a revolutionary cyclotron

The origins of IBA

- We searched, but no industry was interested to build our new cyclotron design
- Therefore, IBA was founded in 1986, as a spin-off of the Cyclotron Research Canter (CRC) of the Catholic University of Louvain in Louvain-la-Neuve (Belgium)
- The initial company ambitions were modest:
  - One cyclotron/year
  - Maximum 15 employees
  - Business of 1.5 to 2 MEuros/year
  - Getting rich was not part of the initial objectives, but having fun clearly was
  - In this respect, we were quite successful!

The IBA Group in 2009

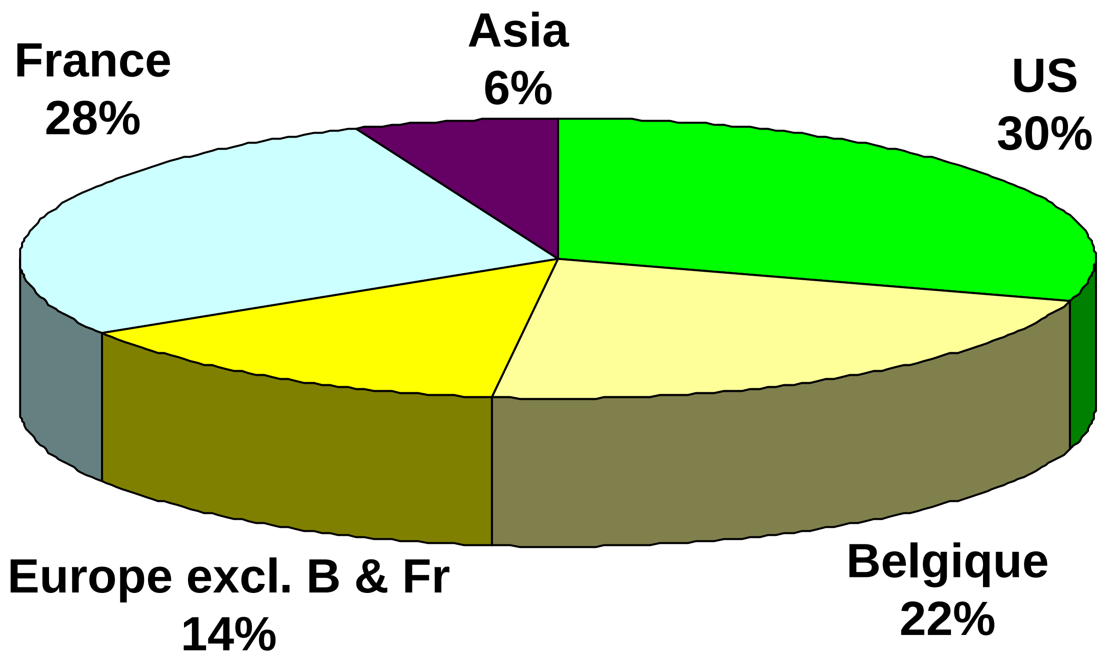
- 2,050 employees in 40 sites on 3 continents
- Turnover > € 330 mio, growing 25% per year
- More than 300 systems (200 Cyclotrons) installed
- Not anymore a cyclotron company, but a company focused on the fight against cancer:
  - Diagnostic: molecular imaging
  - Therapy: Particle therapy & dosimetry

IBA Group Structure: 2050 Employees Worldwide

Corporate: 138

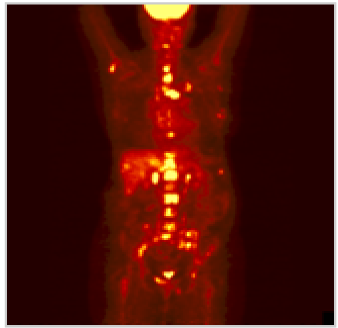
Finance, HR, Legal, R&D, Communication, QA

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



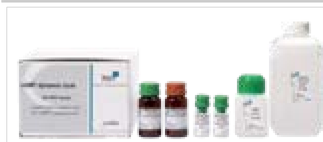
IBA Today: Centering on the fight against cancer

Pharmaceuticals



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

Bioassays
- In vitro medical diagnostics
- Drug screening

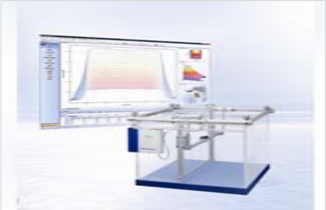


Particle Therapy

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

Dosimetry

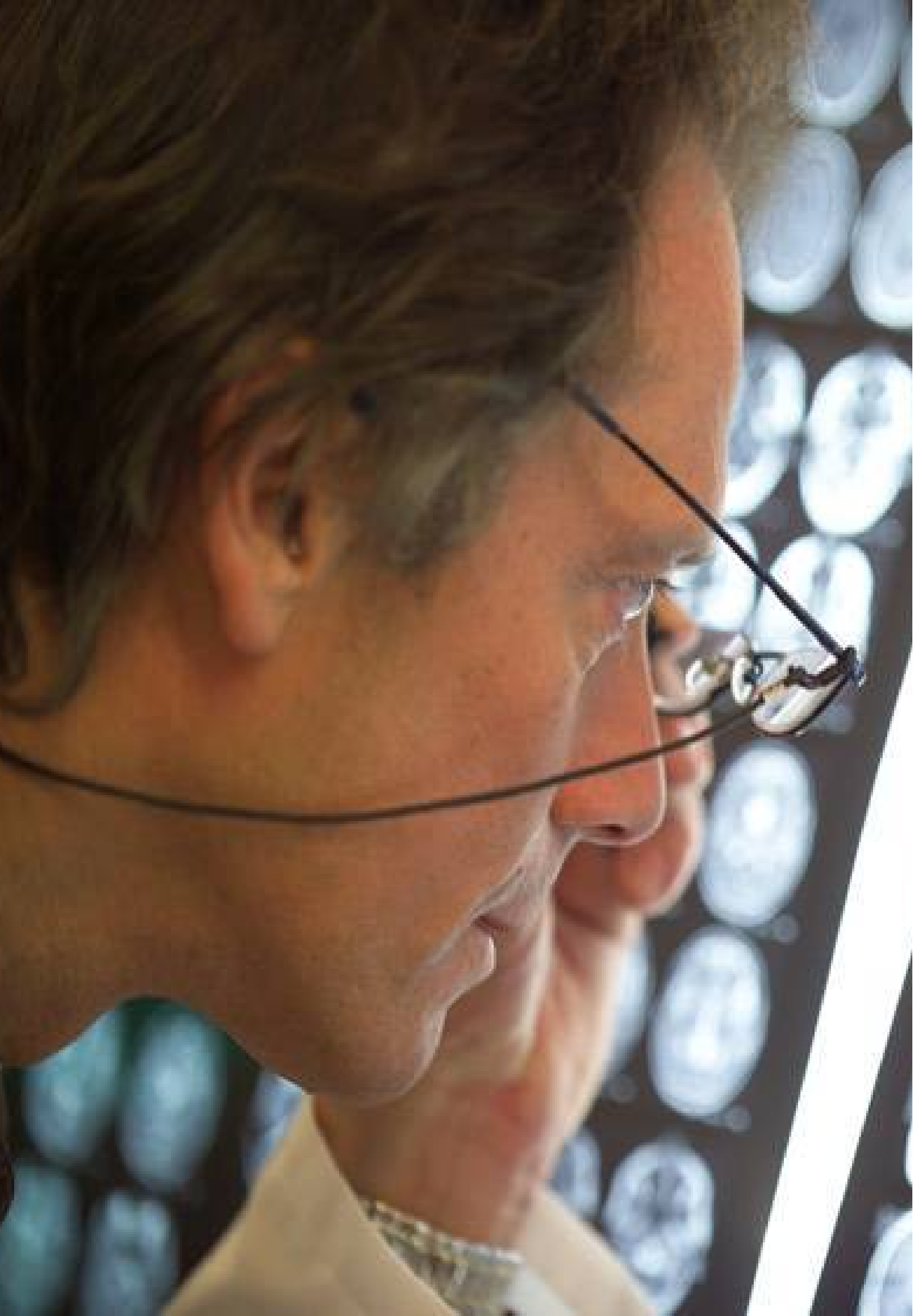
Dosimetry equipment
to measure radiation dose for
- Radiotherapy
- Radiodiagnostics



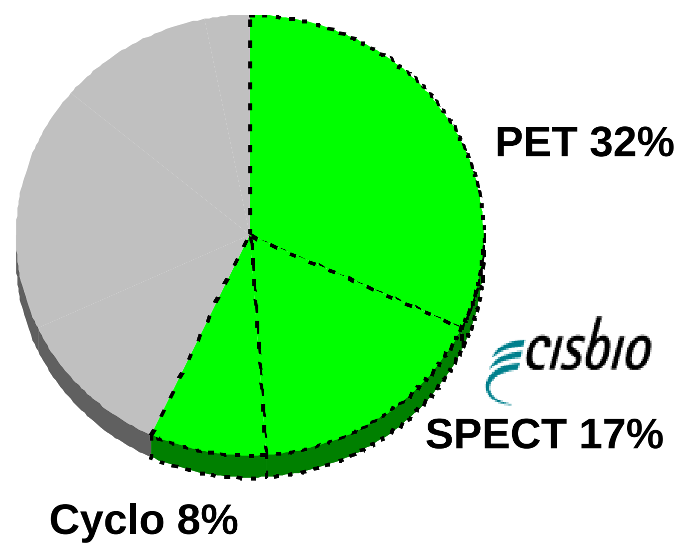
Accelerators

Cyclotrons
- To produces Radioisotopes

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



Iba Molecular

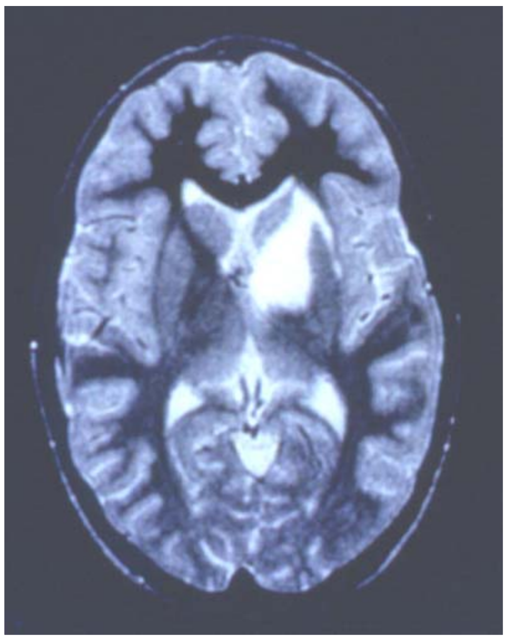


The use of RI for medical imaging

- 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.

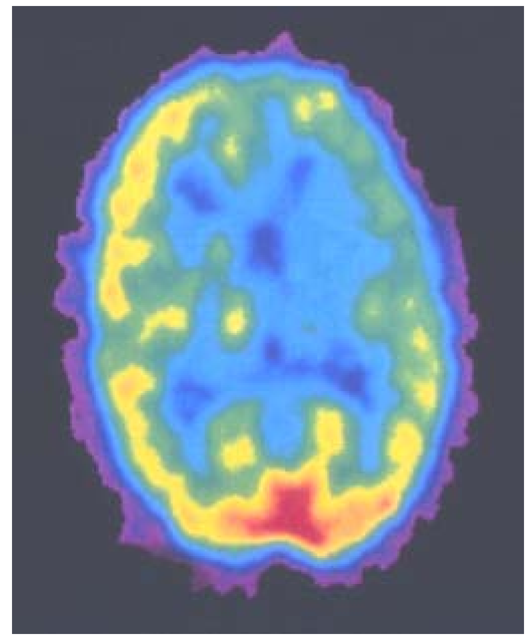
Metabolic vs. anatomic imaging

MRI



Anatomic View

PET



Biological Function

How is imaging done with radiotracers

a) 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 to select a good single photon radiotracer? (a)

The photon energy

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

How to select a good single photon radiotracer? (b)

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 !

ex. 99Mo (66 hours) = 99Tcm (6 hours)

81Rh (4.6 hours) => 81Kr (13sec)

How to select a good single photon radiotracer? (c)

The chemistry

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

example

++ Halogens, Technetium are good

++ Noble metals (Gold) are bad

Nuclear reactions for RI 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)….

“Traditional” nuclear medicine

- Technetium 99m, the most commonly used RI in NM is produced in reactors
- But a number of other, very important NM RI are produced with cyclotrons of higher energy
  - Tl-201 (Cardiac studies)
  - I-123 (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

Positron emission tomography

The positron (anti-electron)

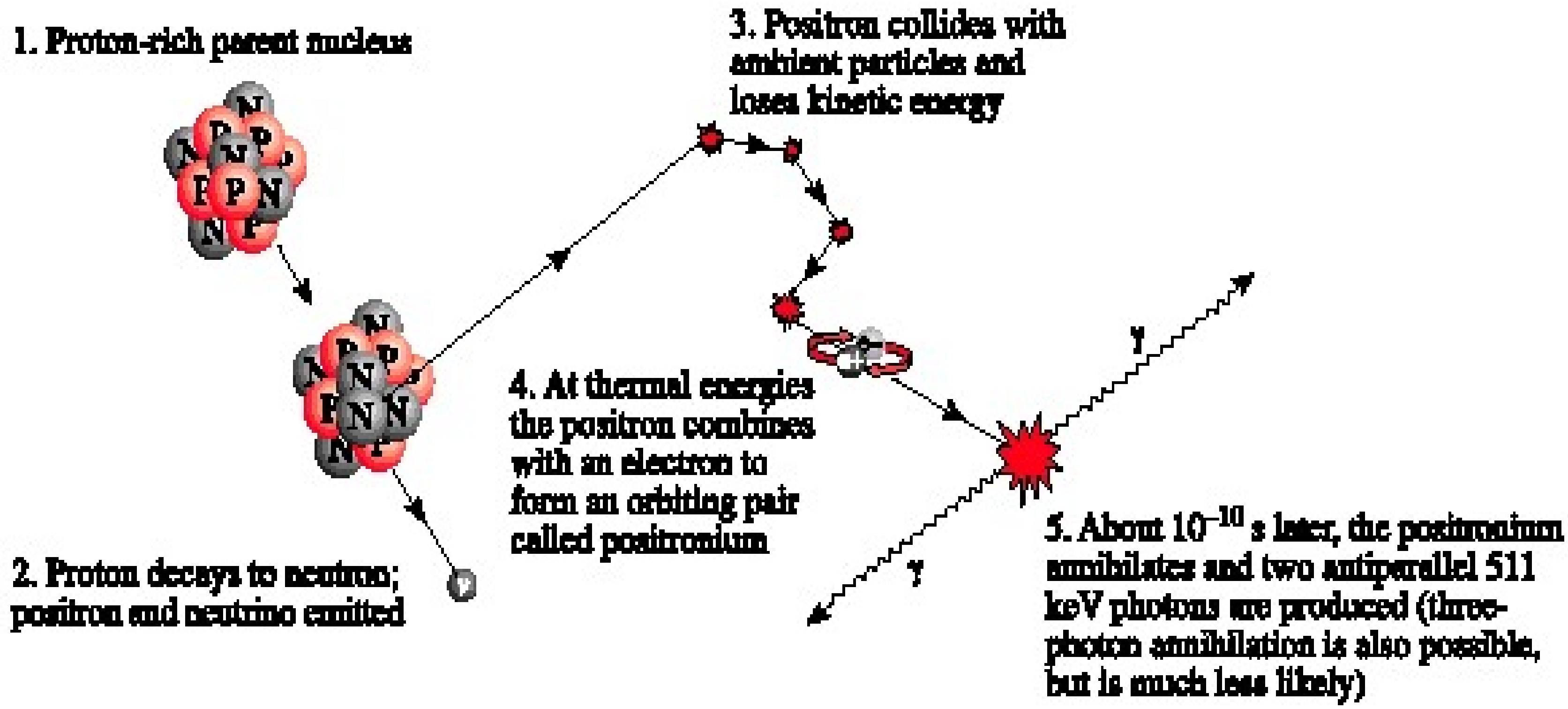


Figure 5. Positron emission and annihilation.

The PET scanner

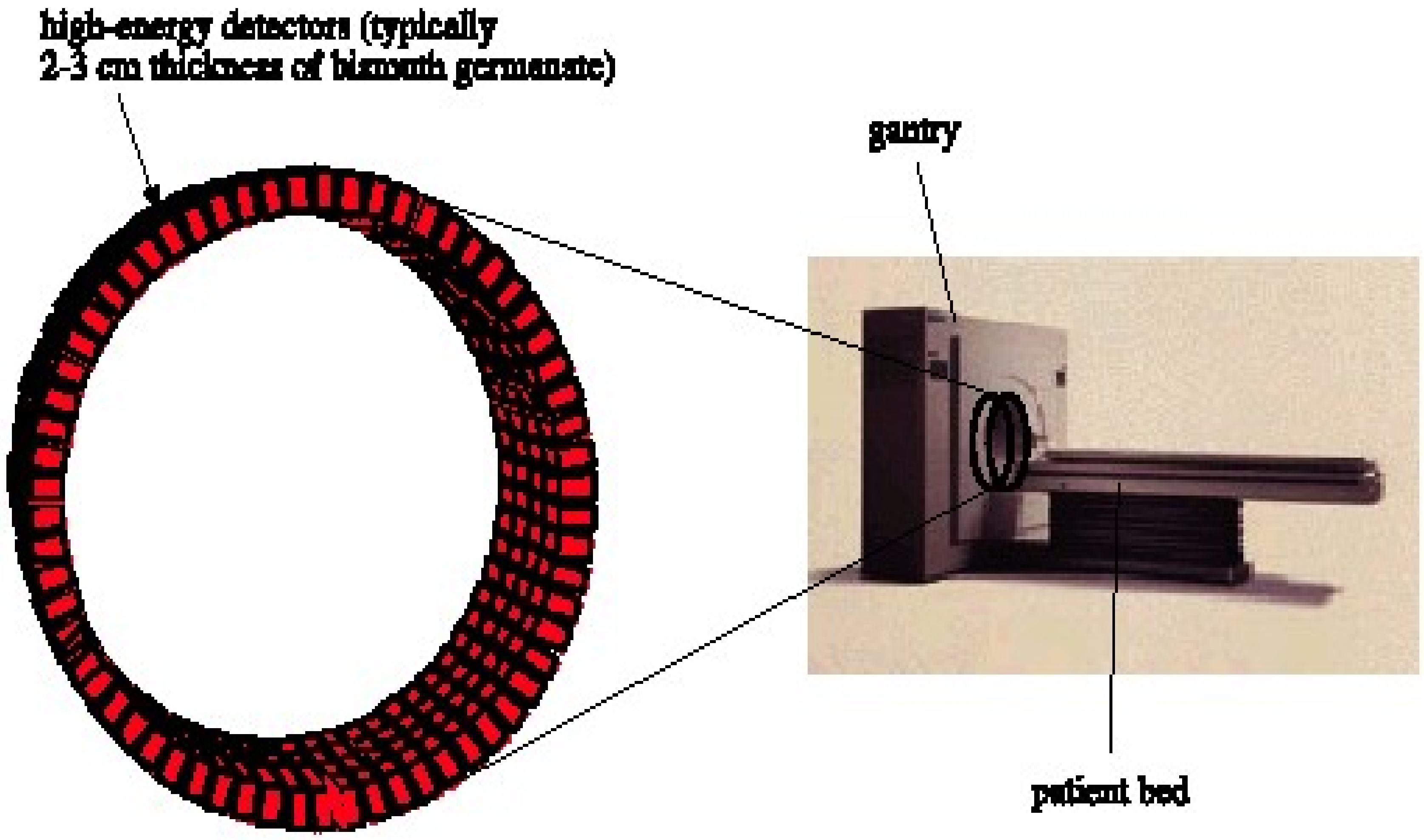


Figure 6. A dedicated PET system (photograph courtesy of CTI, Inc.).

Coincidence detection in a PET scanner

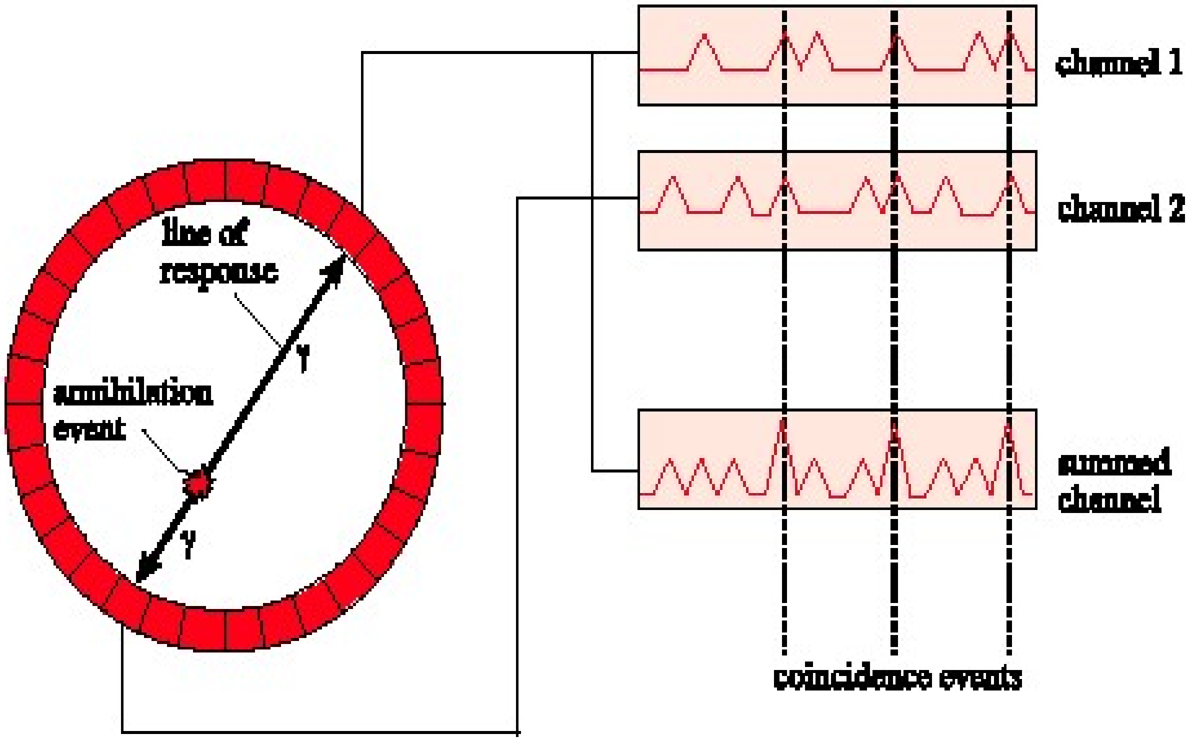


Figure 7. The concept of coincidence detection. If pulses from separate detector elements overlap in time, it is assumed that the detectors registered photons arising from the same annihilation event. In practice, events are assigned digital time stamps, which are compared to find coincidences.

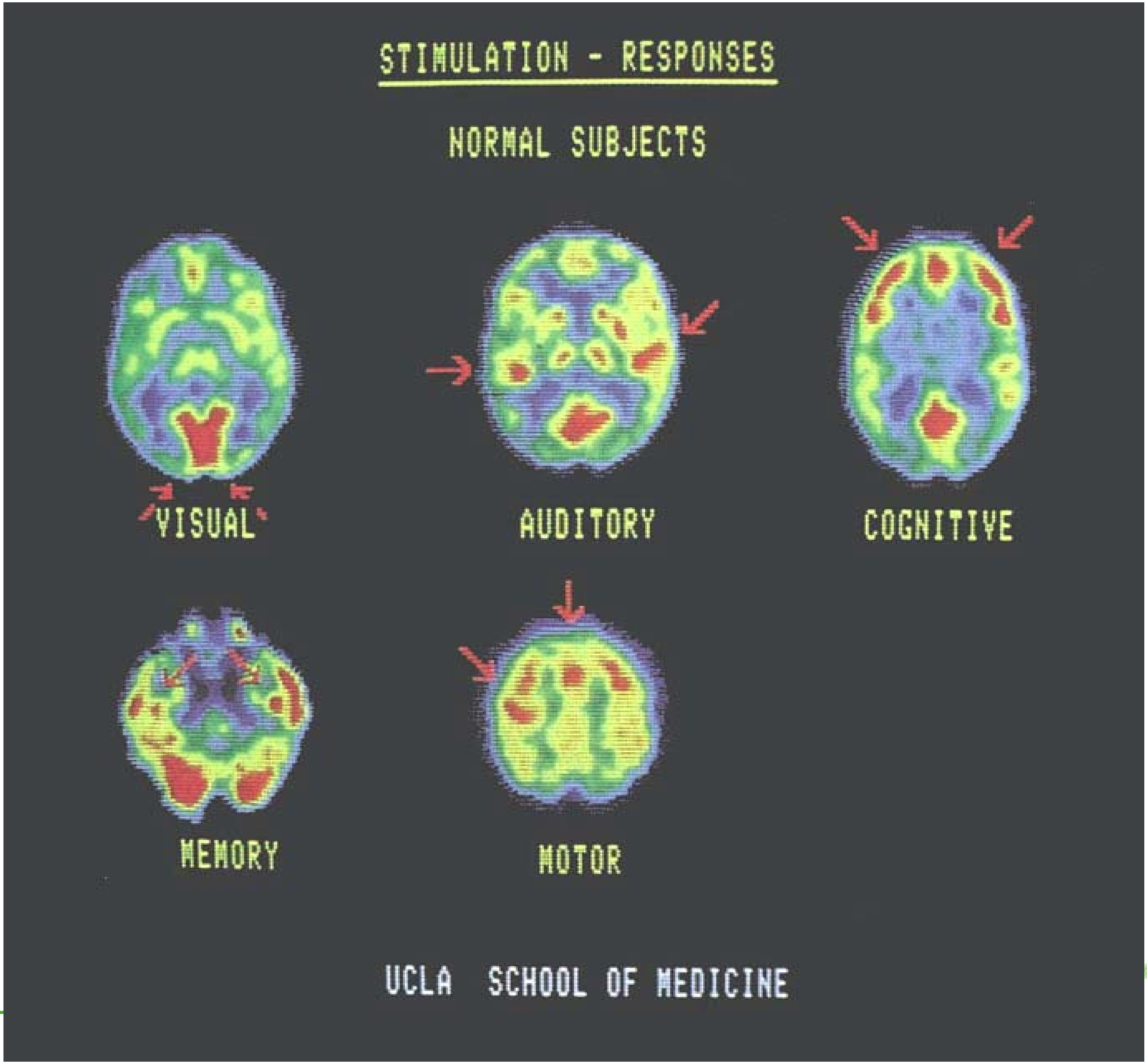
How is imaging done with radio-tracers ?

Positron emitting radio-isotopes

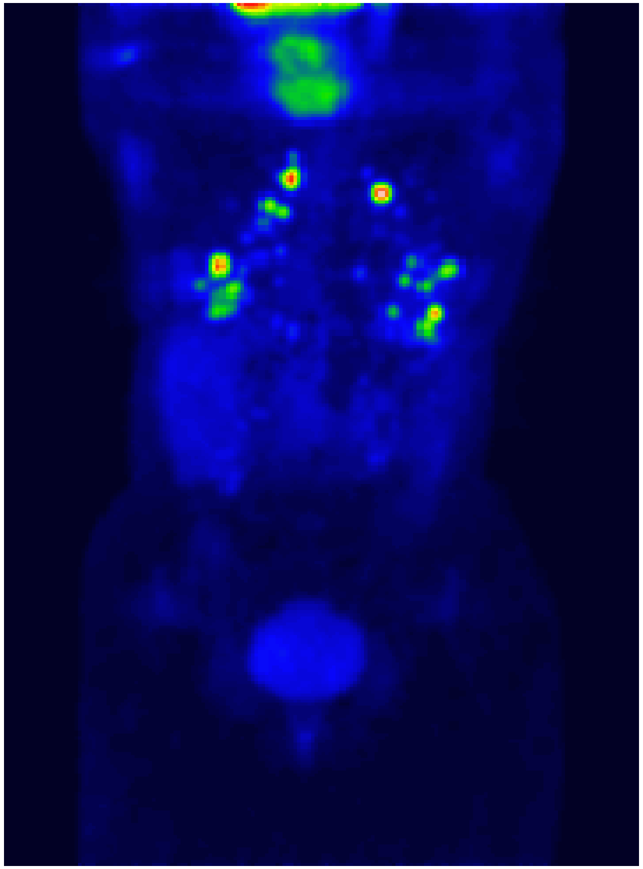
- The emitted positron travels a few millimeters, then meets an electron and annihilates, emitting two photons of 511 KeV at 180°
- These two photons can be detected in coincidence by a ring of detectors surrounding the region of interest
- One knows then that the source of activity is on the line connecting the two detectors
- Several detections allow to locate the source
- By mathematical reconstruction, a 3D representation of the activity can be obtained

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


STIMULATION - RESPONSES
NORMAL SUBJECTS
VISUAL
AUDITORY
COGNITIVE
MEMORY
MOTOR
UCLA SCHOOL OF MEDICINE

Cancer imaging with PET



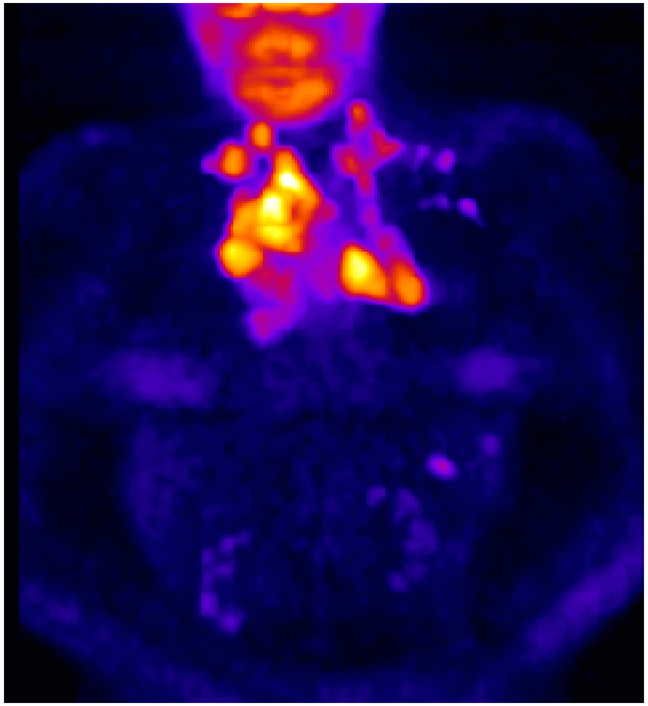
F^{18} FDG

- 45 minute scan time

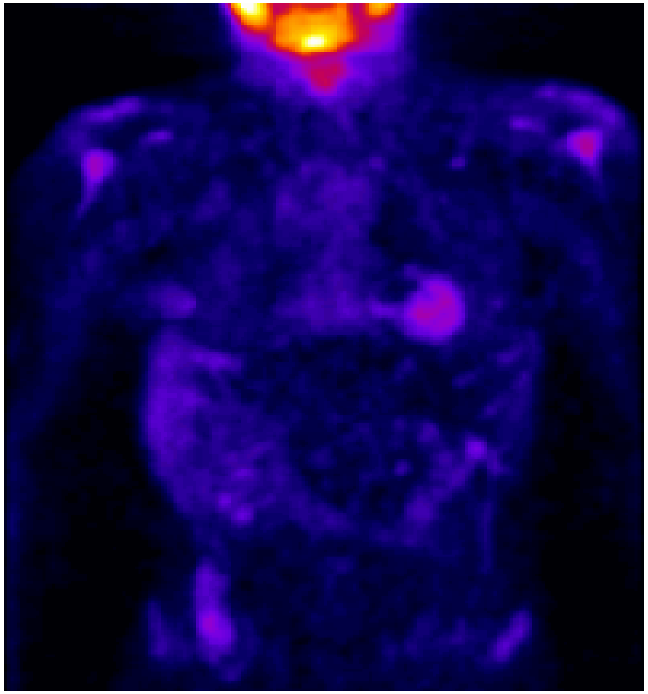
- normal liver & renal
- normal bladder
- metastatic lung lesions

PET Scan - Response to Therapy

31 yr old female with newly diagnosed Non-Hodgkin's Lymphoma



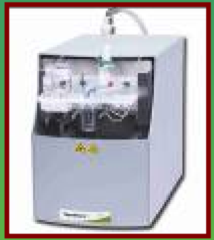
Staging PET Scan



Post Chemotherapy

- 160 PET & SPECT Cyclotrons sold worldwide to Hospitals, R&D centers, Radiopharma. companies

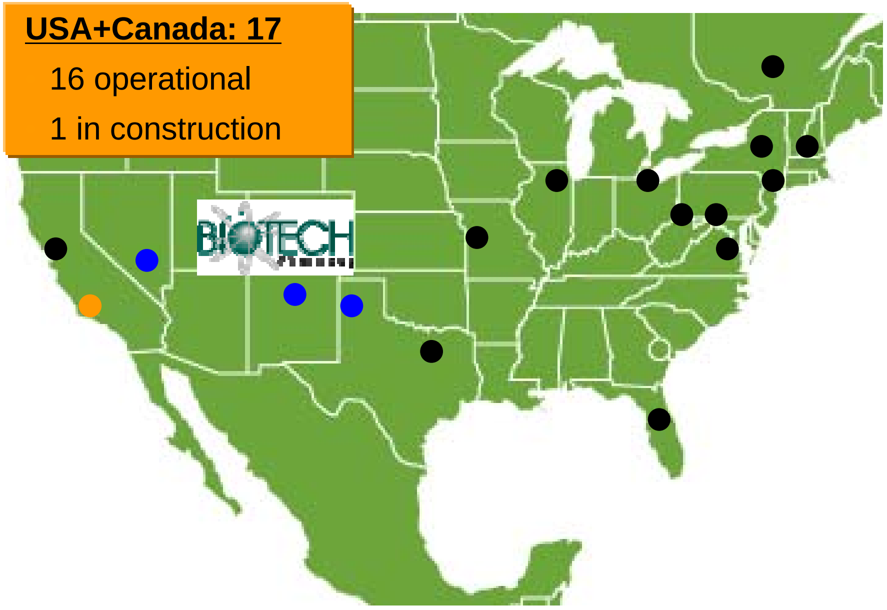
33 facilities Worldwide producing Radiopharmaceuticals…

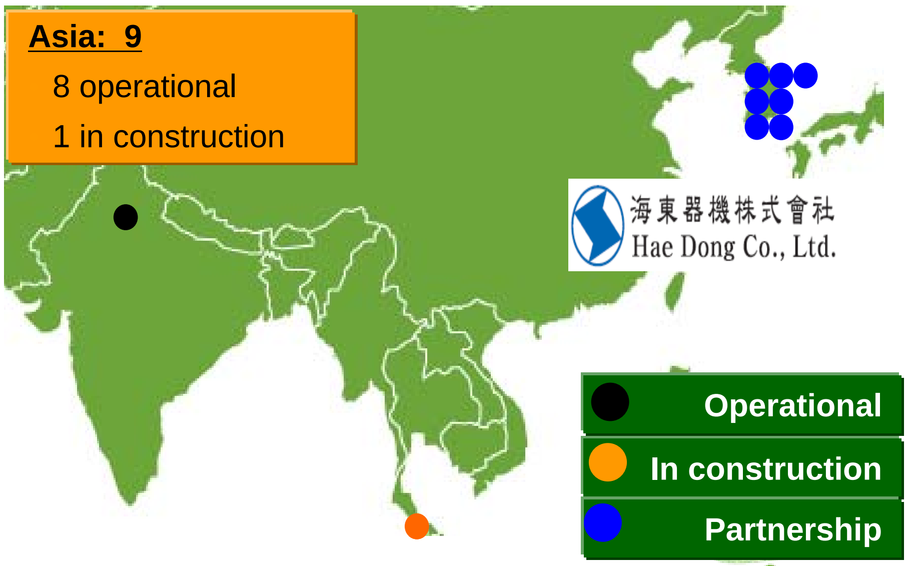


… distributed daily to hospitals

52 PET Radiopharmaceuticals Production Facilities

- Alliances to enlarge network for distribution of future new drugs





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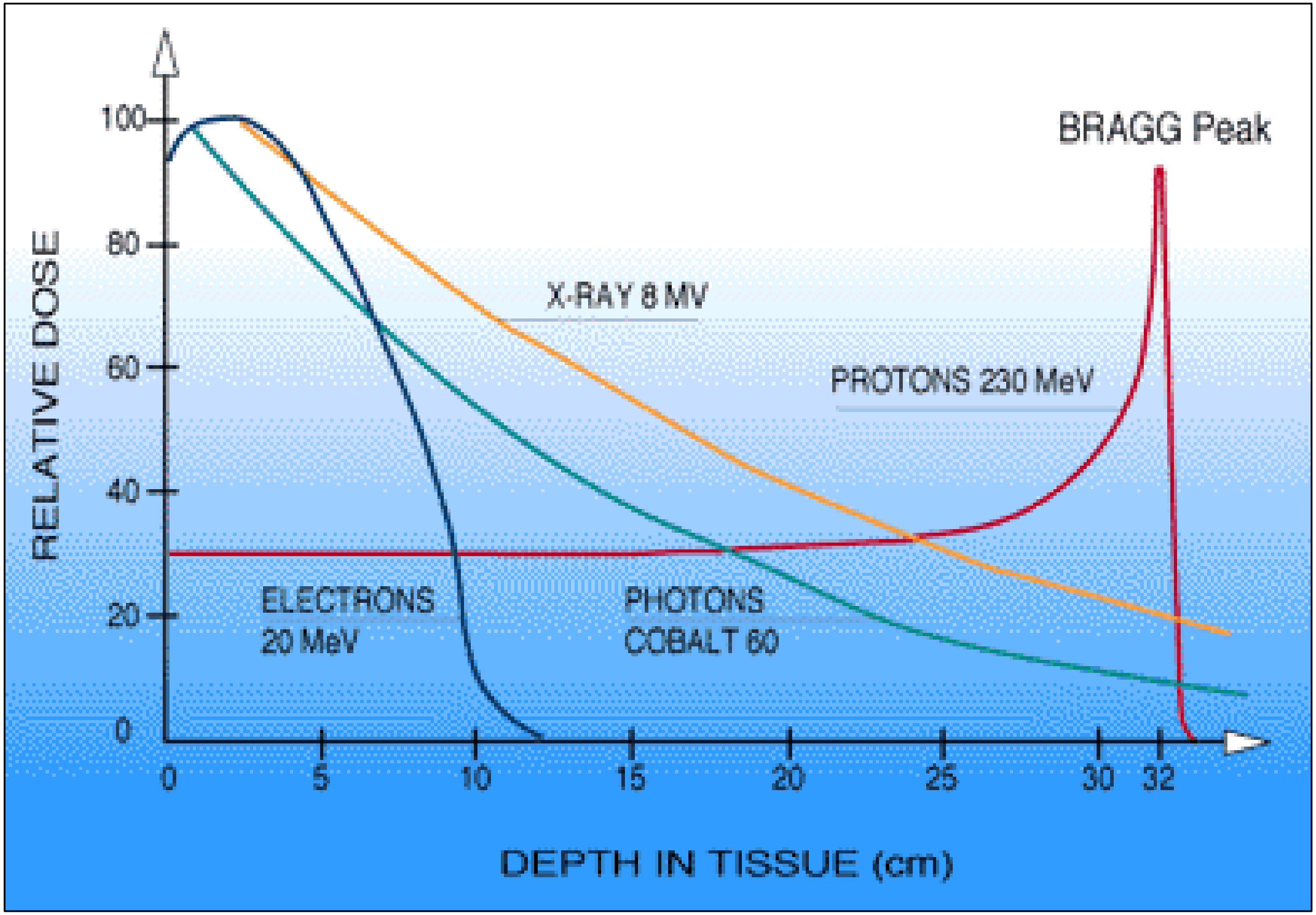
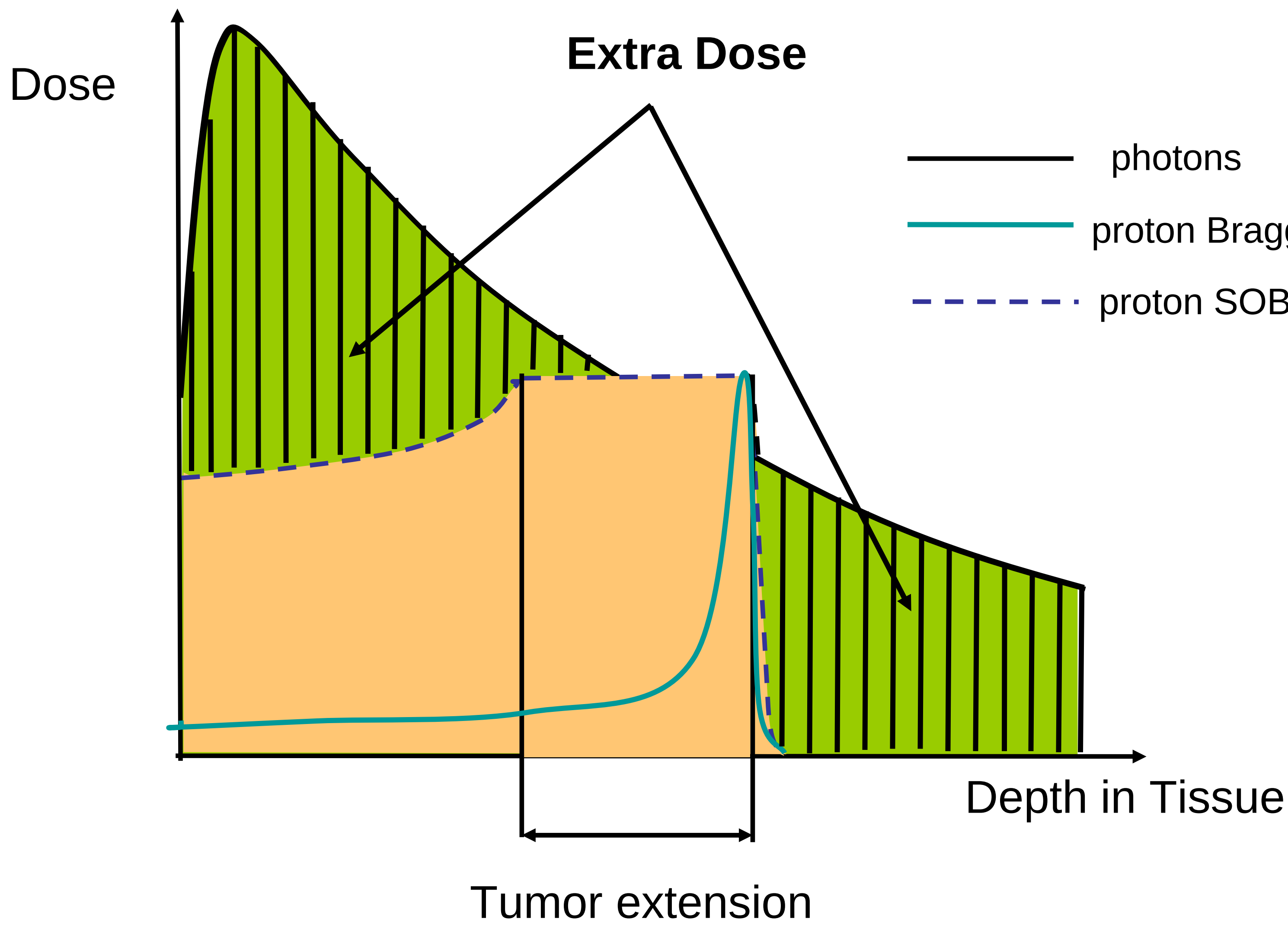
Proton therapy

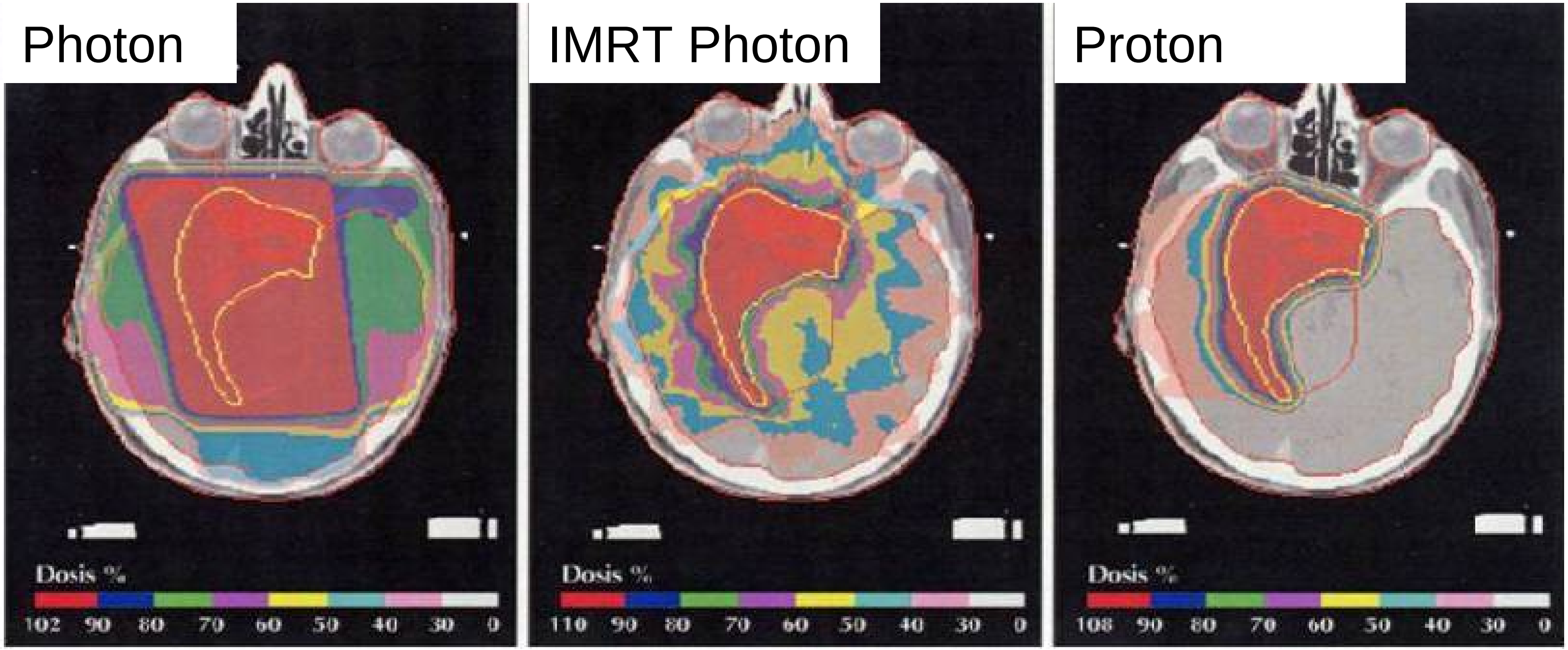
The depth dose curve distributions



Photon-Proton dose distribution comparison



Particle Therapy: Comparing PT & Conventional RT

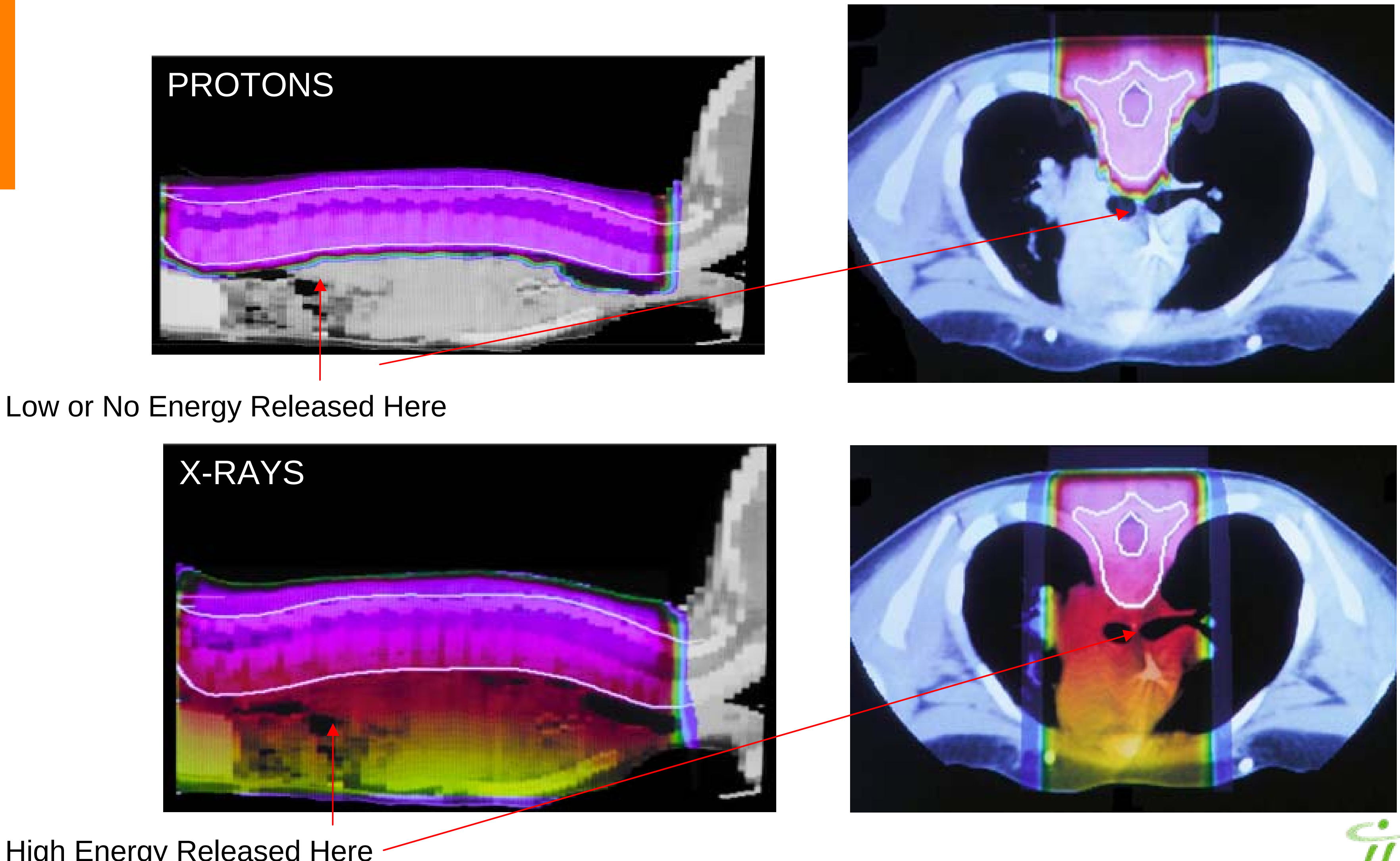


Conventional Radiotherapy

IMRT = Intensity Modulated Radio Therapy

Scattering technique

Medulloblastoma Treatment X-Rays vs Protons



Proton thérapy center

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

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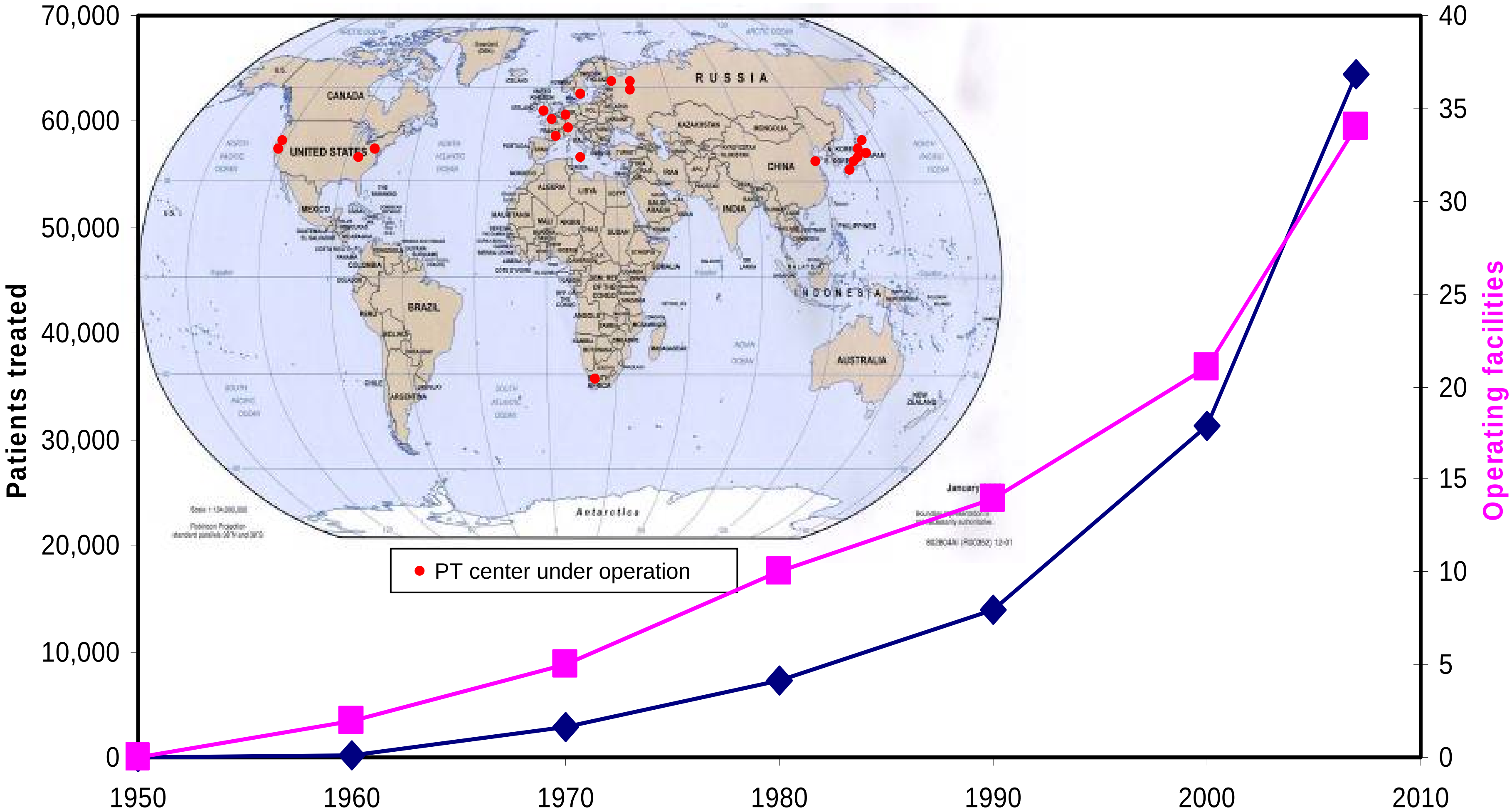
IBA Proton Therapy System

- 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!

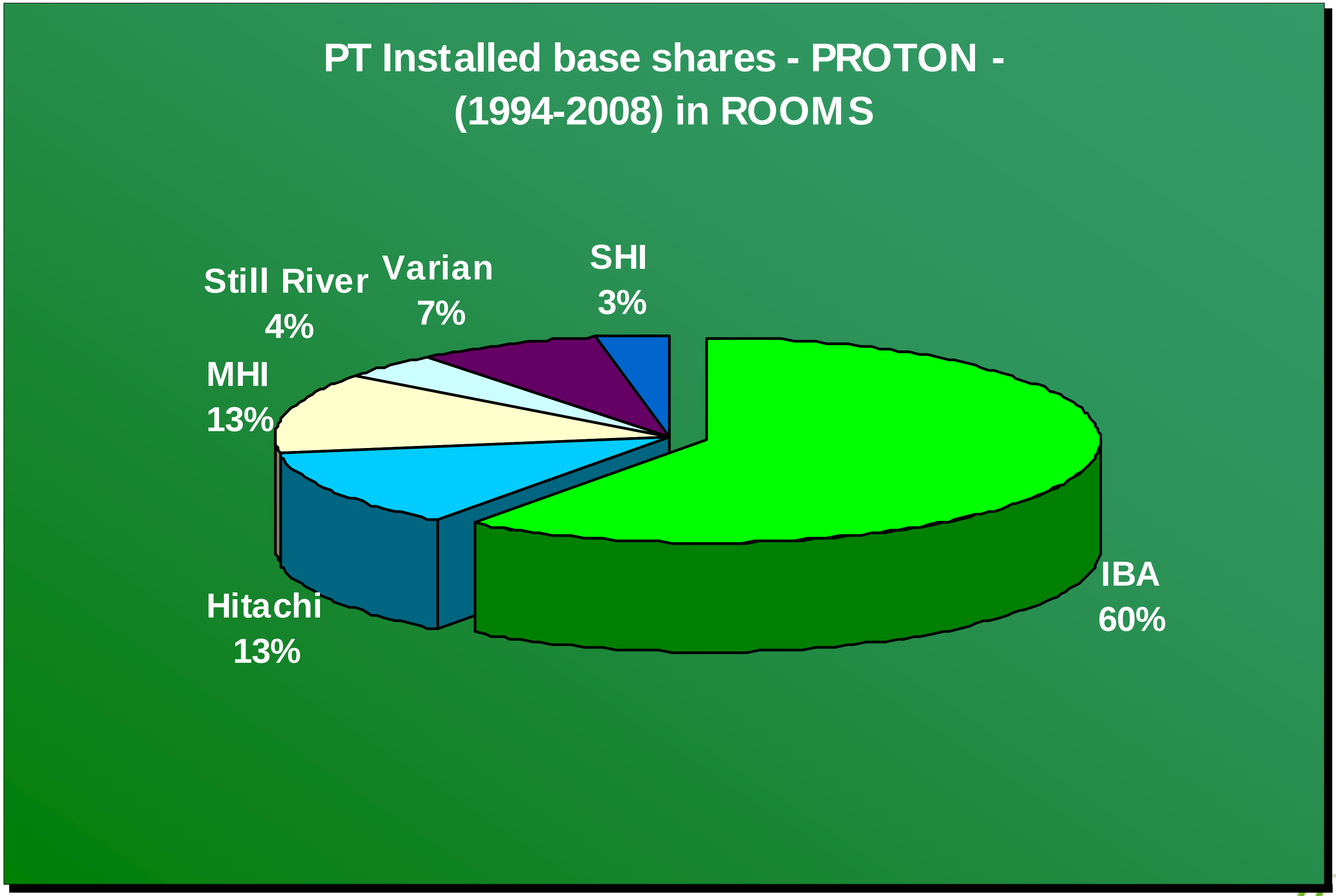
Proton Therapy is growing rapidly!



Courtesy Janet Sisterson & PTCOG

13 IBA PT customers in the world

IBA has currently the largest installed base in PT



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

iba Particle Therapy

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

iba Particle Therapy

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

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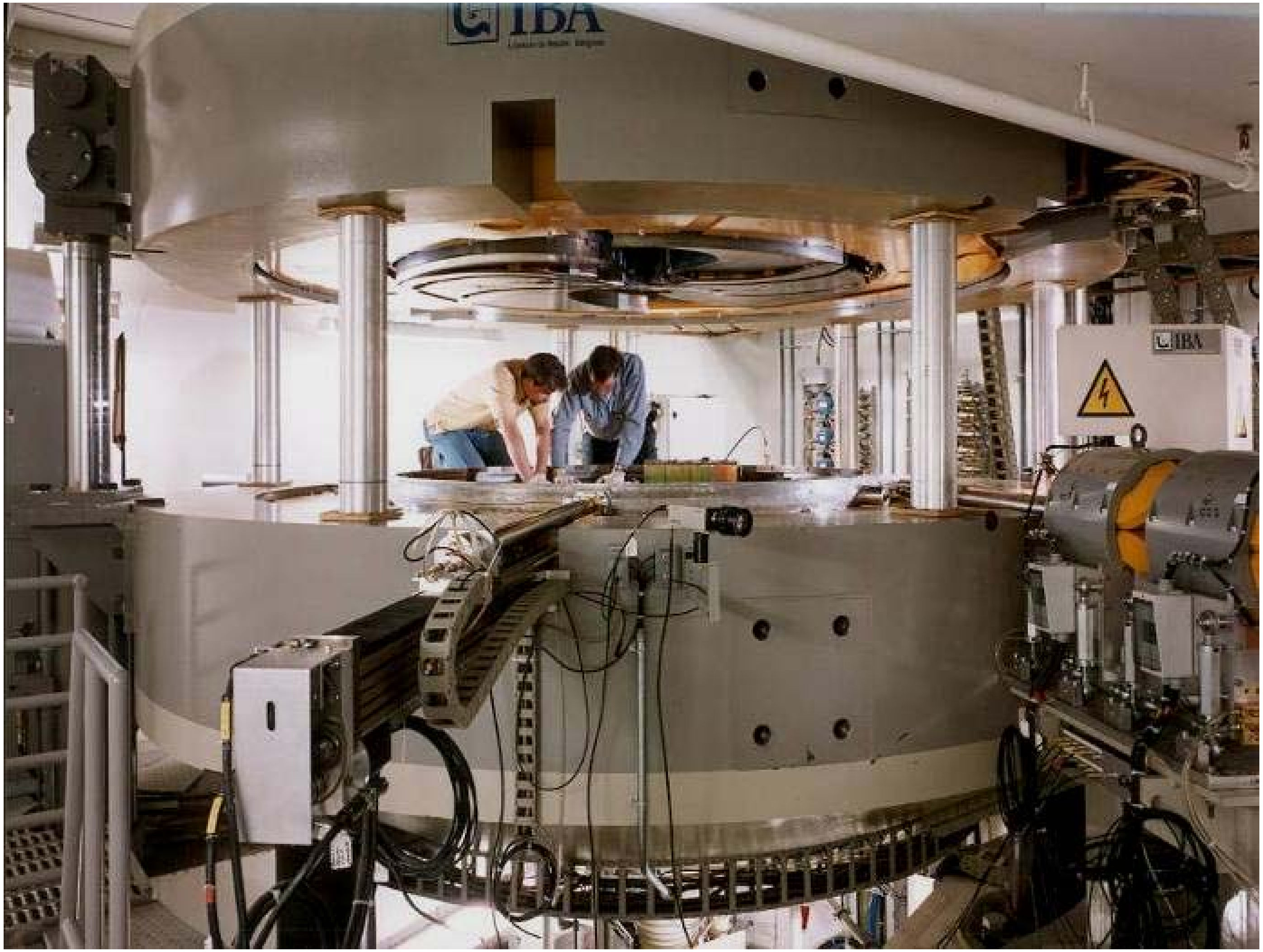
Hampton University Proton Therapy Institute

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

Main IBA PT subsystems

The Proteus-235 Cyclotron

The cyclotron opens at median plane for service



Inside the cyclotron

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The ion source and central region

The energy selection system

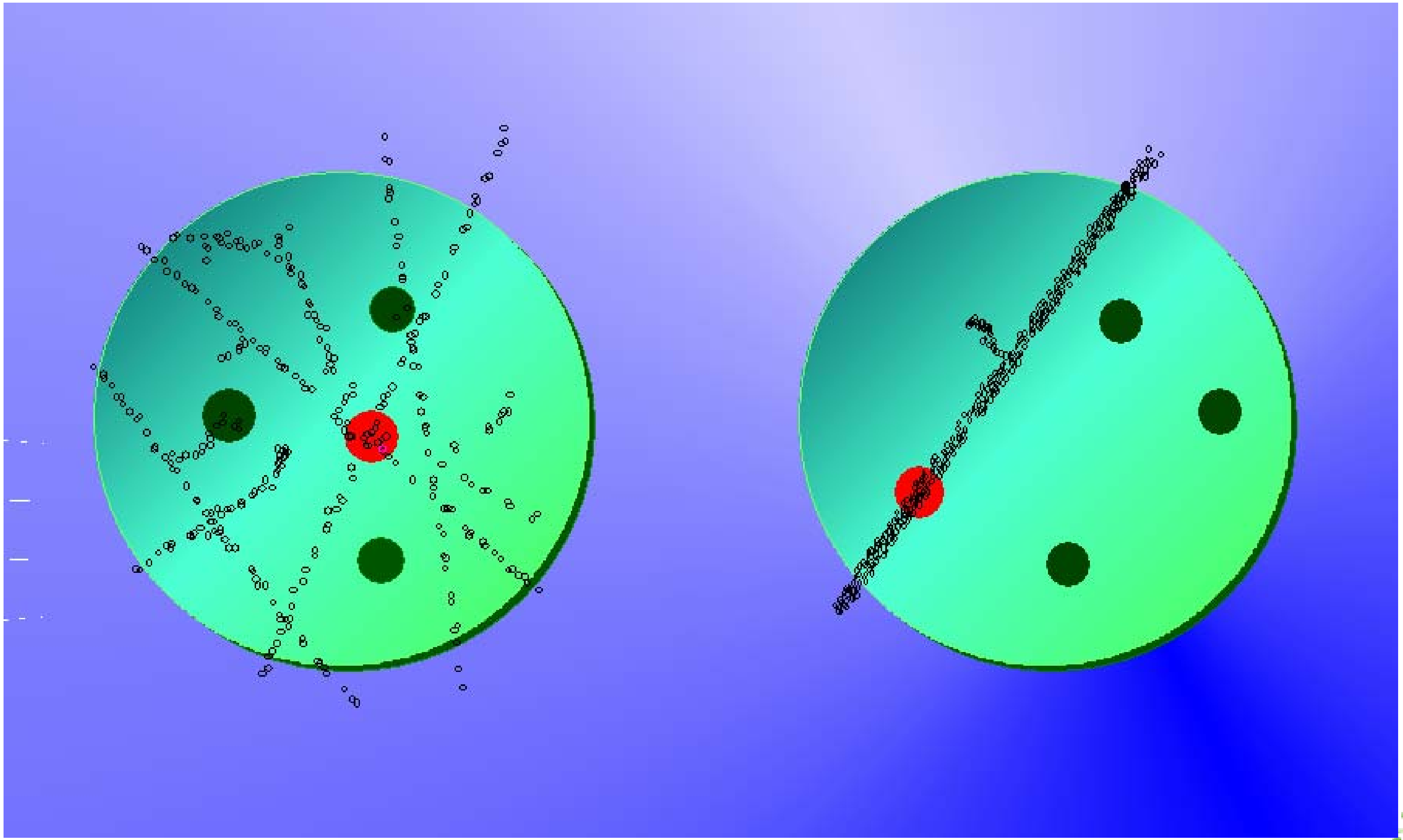
Carbon beam therapy

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

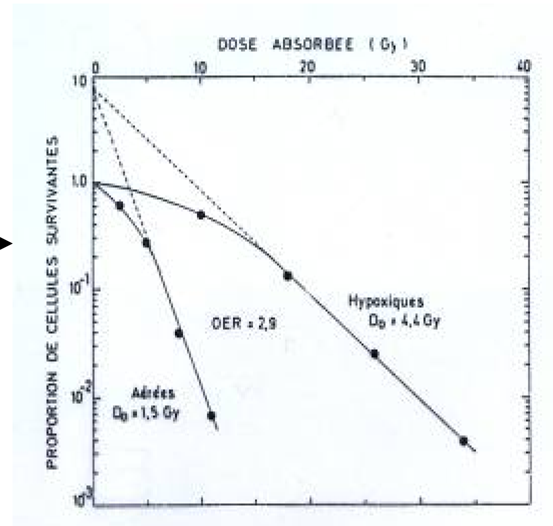
Photons, Protons — Neutrons, Carbon ions

Low LET — High LET



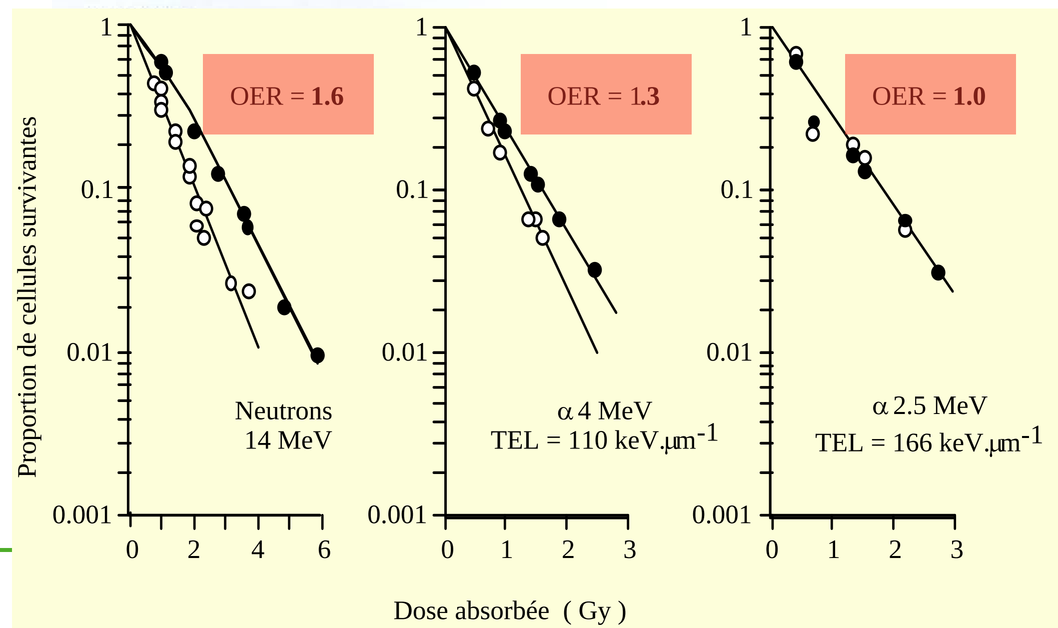
Oxygen Enhancement Ratio

Low -LET



OER decreases as the LET increases

High -LET



Fractionation with Carbon ions

- Cell repair (and dependence on the mitotic cycle) is significantly reduced with carbon ions
- For this reason, less fractions can be justified
- In treating non small cells lungs tumors, Dr. Tsujii from NIRS obtained increased local control with low morbidity by reducing the number of fraction from 18 to 9, 6, 4, 2 and now 1 fraction. He has now treated more than 100 patients with one fraction.
- NIRS currently uses also 2 fractions for liver tumors, and more fractions (10 to 15) for other sites like soft tissue sarcoma and prostate

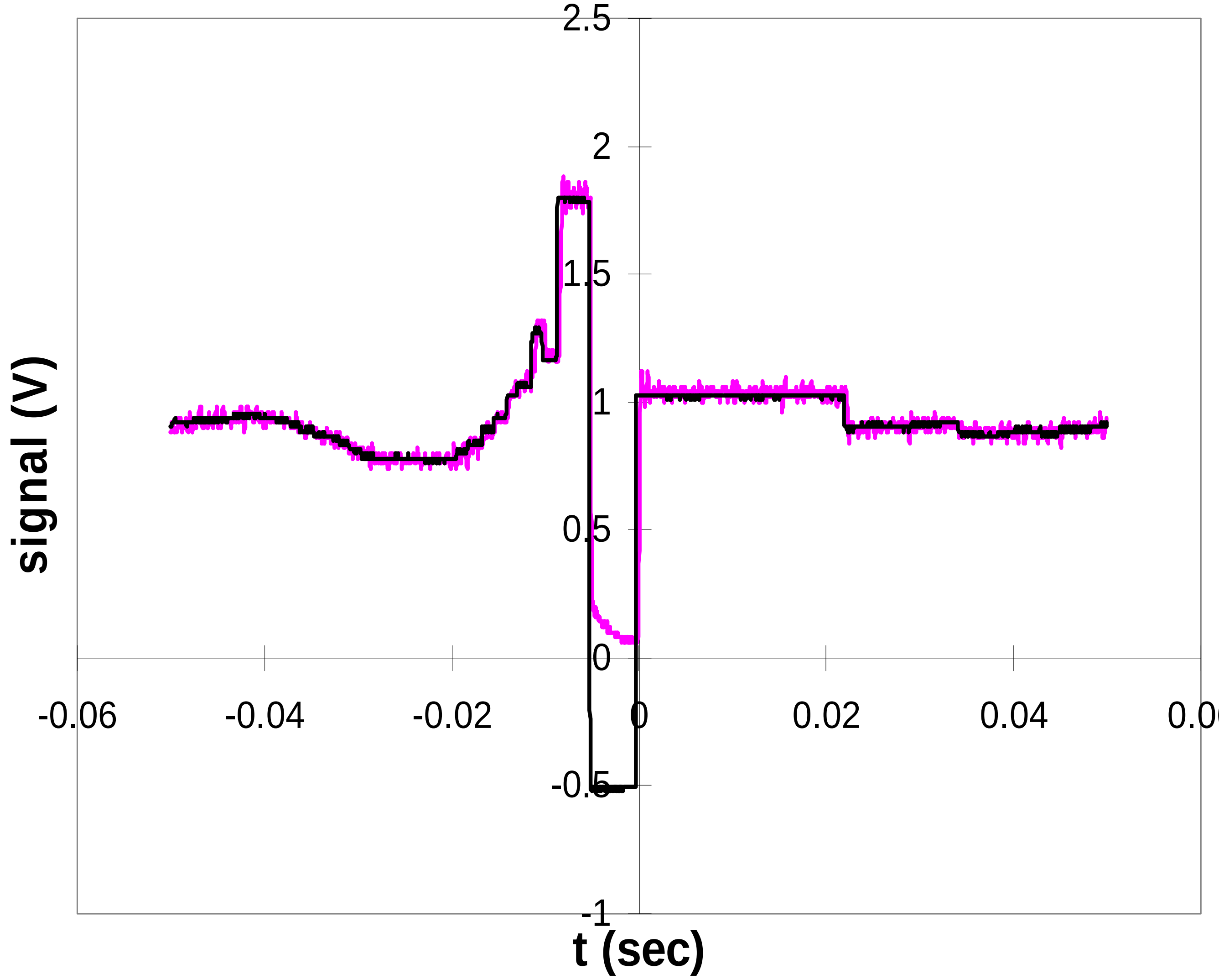
Are carbon ions always better? NO!

- Carbon ions are more effective than protons on radio resistant tumors
- Carbon ions will be preferred when the tumor is more radio resistant than the surrounding healthy tissues
- But Carbon ion will be avoided when the tumor is equally or more radiosensitive than the surrounding healthy tissues
- Therefore, all Carbon therapy facilities also have the possibility to use protons

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)
- 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

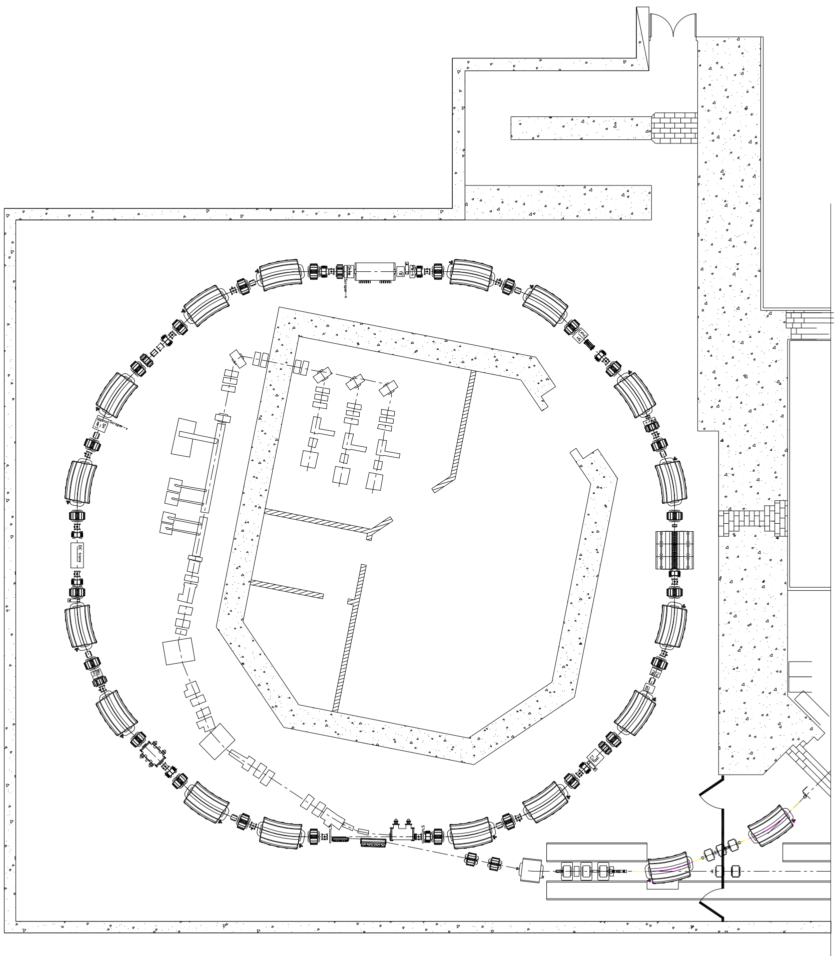
Real oscilloscope measured signals

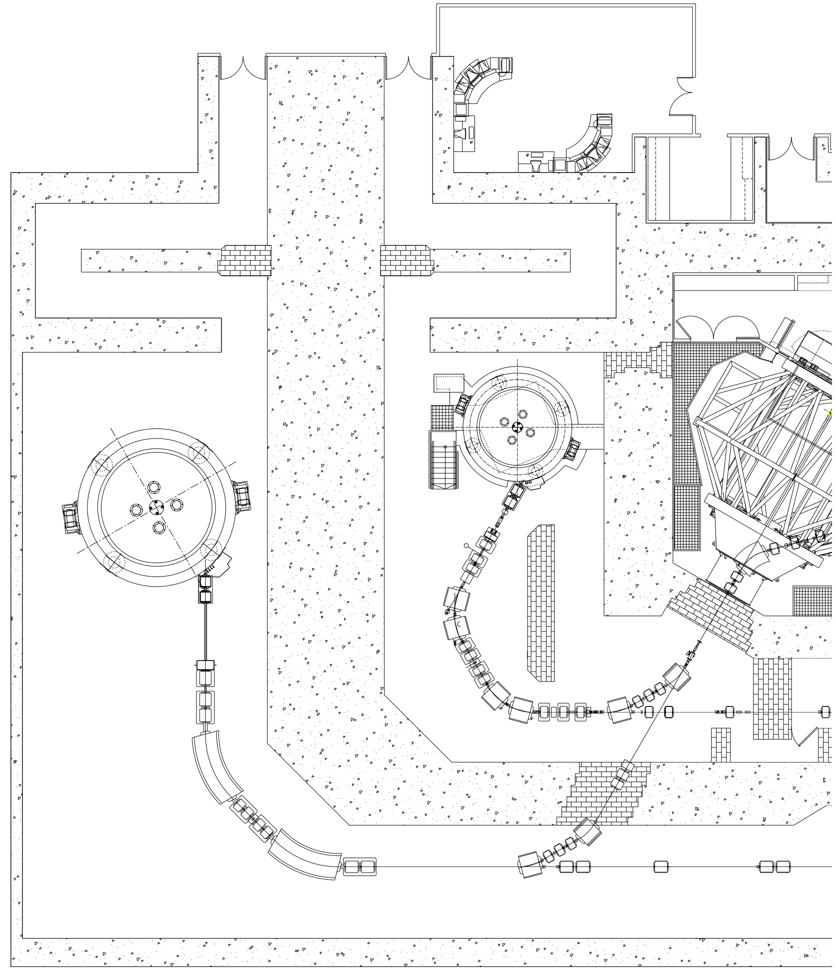


Change of energy?

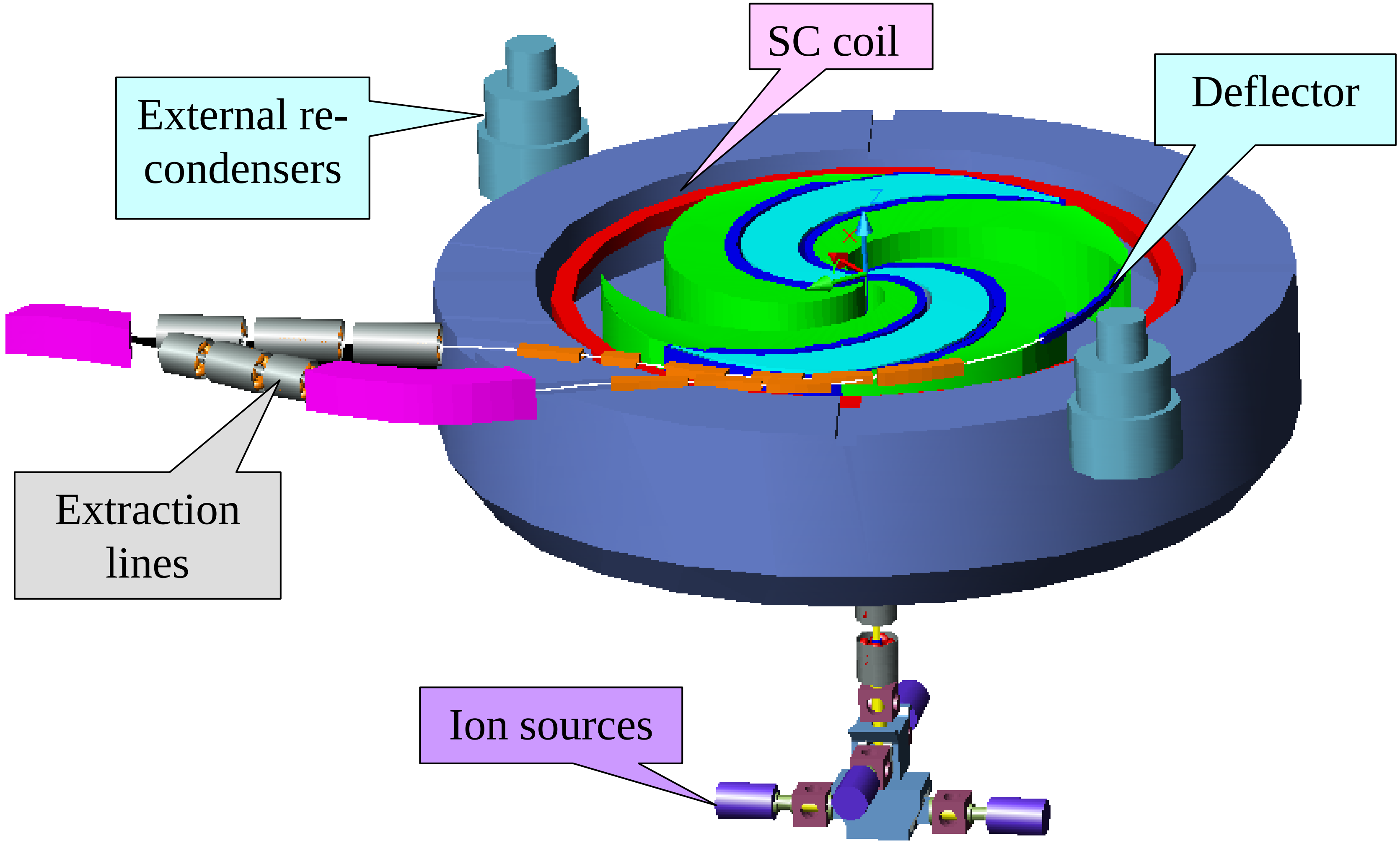
- Cyclotrons are simpler at fixed energy
- Energy change by graphite degrader at waist after cyclotron exit, followed by divergence slits and energy analyzer
- This very effectively decouples the accelerator from the patient
- Fragmentation products are effectively eliminated in slits and ESS
- Yes, 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. But respiration cycle is 2…4 seconds, so 100 msec is fine

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





Cyclotron view



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)

Status of the cyclotron

- On April 22 & 23 2009, an international design review was organized by IBA
- A team of experts in superconducting cyclotrons from various countries was invited for a 2 days, in depth review of the design
- The results of the review were completely positive, and no “show-stoppers” were found
- The design has now reached a stage where long lead items (steel, superconducting coils) can be ordered. Contracts for these are ready to be signed
- Sigmaphi (Vannes) has been selected for the design and construction of the superconducting coils
- As soon as the agreements with Archade are finalized, IBA will start the construction of the prototype

The commercial landscape (a)

- The prototype hospital based carbon therapy facility was built by GSI in Heidelberg: HICAT. The control software is provided by Siemens.
- The synchrotron is working, and beam is available in the treatment rooms, but the Siemens software is delayed
- The IP from HICAT was transferred from GSI to Siemens, and Siemens obtained two additional orders in Marburg and Kiel
- Another system (CNAO) is built by national labs in Italy. It is based on the CERN-TERA PIMMS design. The synchrotron is today under assembly
- A CNAO-like system will be built in Austria (Med-Austron) by an association of physics laboratories

iba Particle Therapy

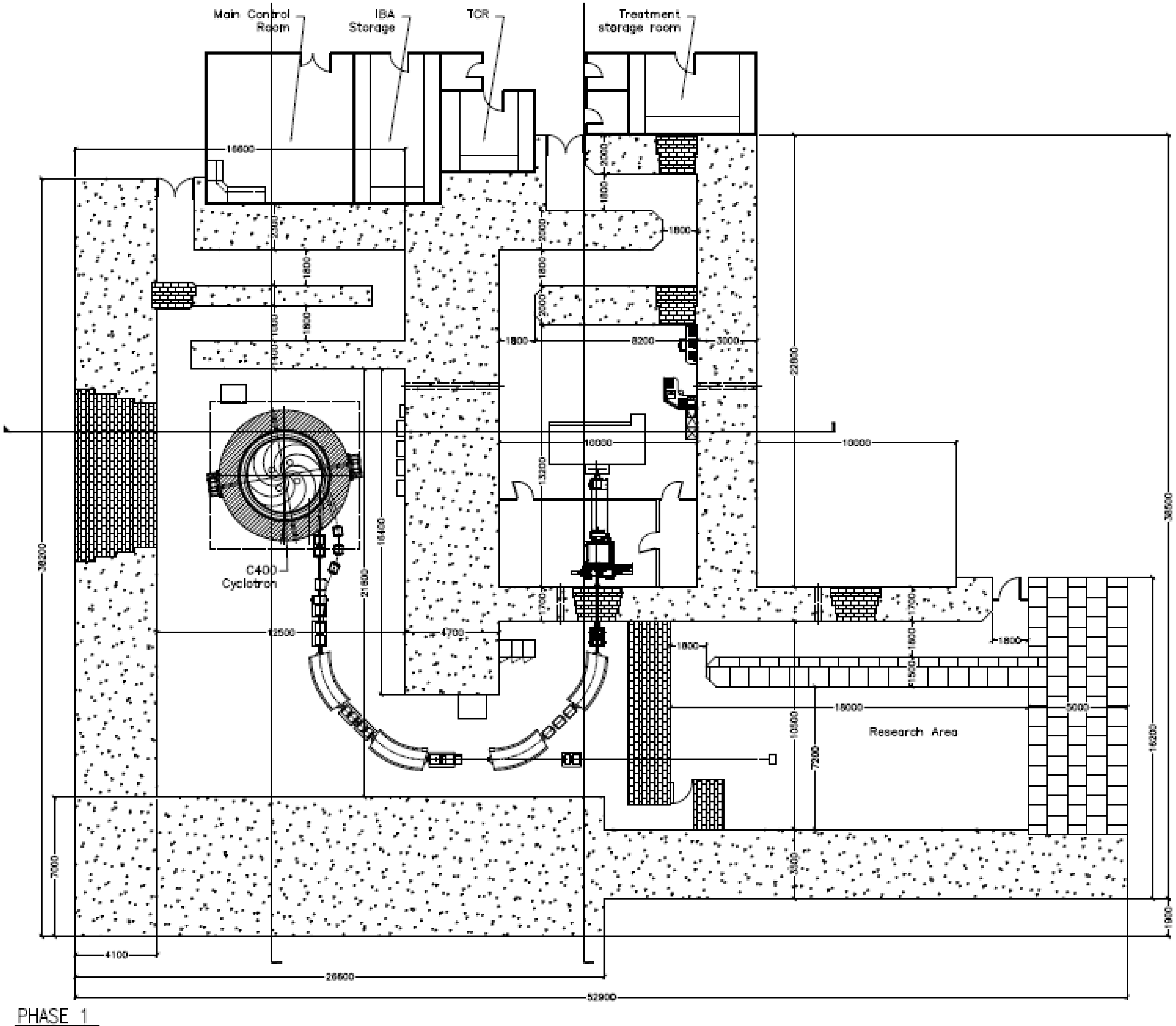
The commercial landscape (b)

- Tenders are ongoing in Lyon (France) (Etoile) and in Mayo clinic (Rochester), but they progress slowly.
- Siemens announced that they were encountering problems and delays to complete the control software in Heidelberg, and they decided to pull out (temporarily) (?) from the market.
- In Etoile, a French temporary association of companies is offering a synchrotron solution licensed from the CNAO system
- In Japan, NIRS is developing a hospital sized carbon therapy system. The prototype is installed at Gunma University. This technology will be available to Japanese manufacturers

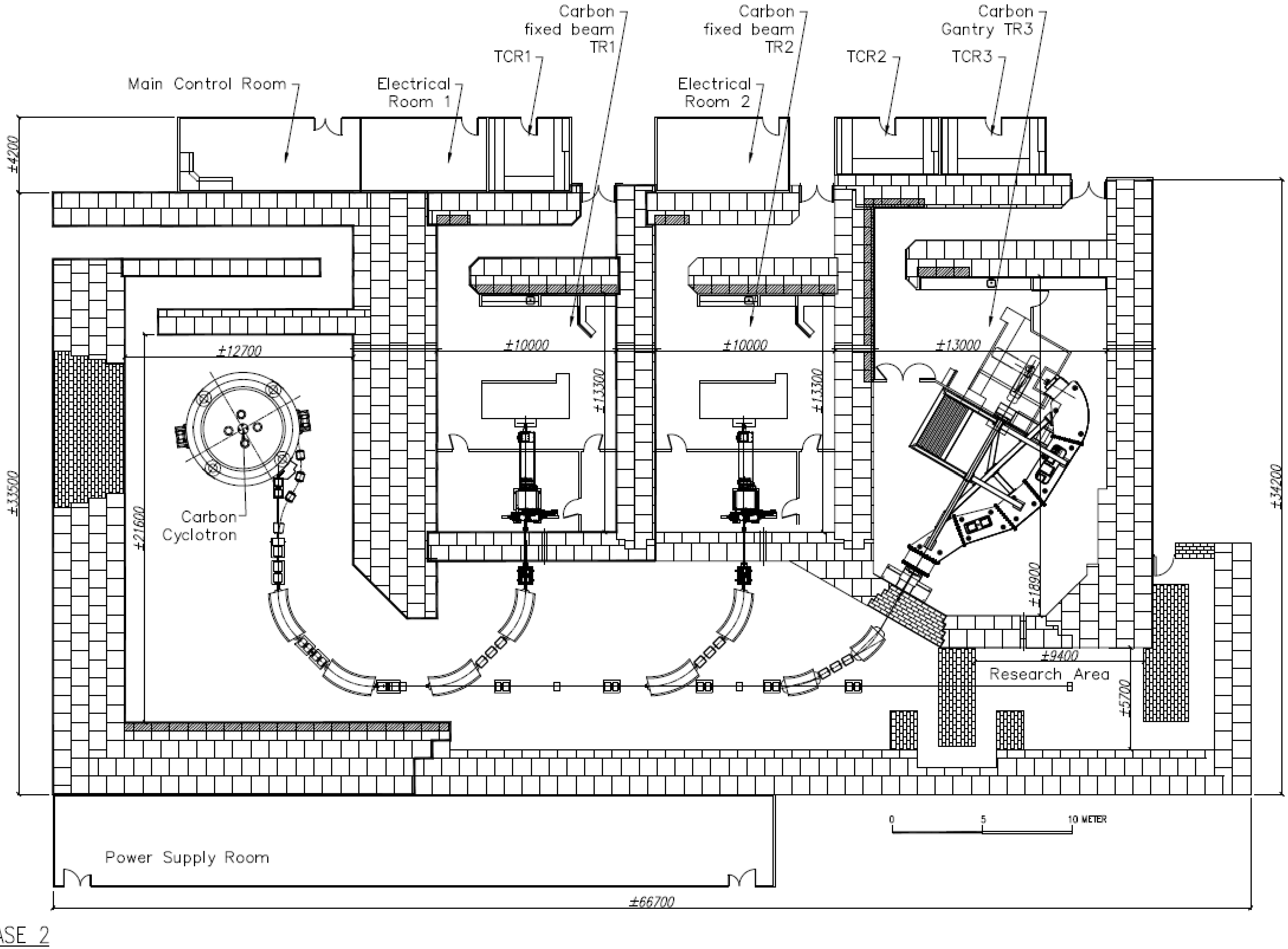
The agreement with Archade (Caen)

- IBA will install the C400 prototype in Caen, close to the GANIL laboratory, within the frame of a research project with ARCHADE.
- Within the frame of this research project, the region will finance the building and electricity, and eventually buy the prototype.
- Archade will hire, and IBA will pay 9 to12 scientists to work on radiobiology and hadron therapy related physics issues to contribute to a carbon TPS.
- 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



Particle Therapy

Thank you…