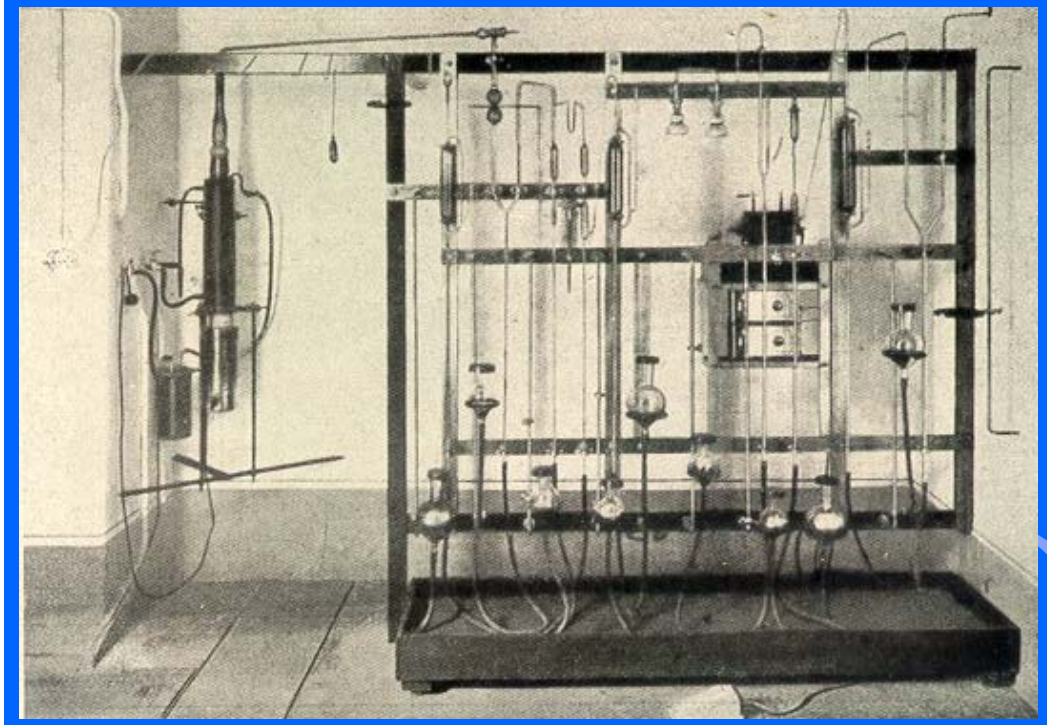
Medical Physics: from Via Panisperna to hadrontherapy

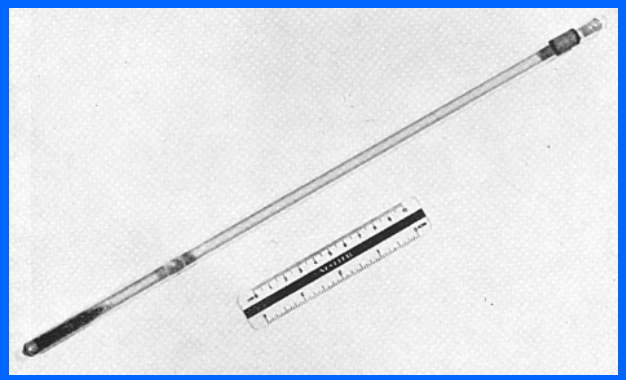
Ugo Amaldi

University Milano Bicocca and TERA Foundation

The patent on the efficacy of slow neutrons and the "tube"

1934 : Fermi discovery was made with a Be-Rn source. Radon extracted at Laboratorio Fisico della Sanità Pubblica





The “Divine Providence”

The third paper

RADIOATTIVITÀ « BETA » PROVOCATA DA BOMBARDAMENTO DI NEUTRONI. — III.

E. AMALDI, O. D'AGOSTINO, E. FERMI, F. RASETTI, E. SEGRÈ

« Ric. Scientifica », 5 (1), 452–453 (1934).

Sono state proseguite ed estese le esperienze di cui alle Note precedenti [1] coi risultati che ricordiamo appresso.

Idrogeno – Carbonio – Azoto – Ossigeno. – Non dànno effetto apprezzabile. Sono stati esaminati paraffina irradiata al solito modo per 15 ore con una sorgente di 220 mC, acqua irradiata per 14 ore con 670 mC e carbonato di guanidina irradiato per 14 ore con 500 mC.

Fluoro. – Il periodo del Fluoro è sensibilmente minore di quanto indicato precedentemente e cioè di pochi secondi.

Magnesio. – Il Magnesio ha due periodi, uno di circa 40 secondi e uno più lungo.

Bromo. – Ha due periodi, uno di 30 minuti e l'altro di 6 ore. L'attività corrispondente al periodo lungo e probabilmente anche l'altra, seguono chimicamente il Br.

Palladio. – Periodo di alcune ore.

Jodio. – Periodo 30 minuti. L'attività segue chimicamente lo Jodio.

Praseodimio. – Ha due periodi. Uno di 5 minuti e l'altro più lungo.

Neodimio. – Periodo 55 minuti.

Samario. – Ha due periodi uno di 40 minuti e uno più lungo.

Oro. – Periodo dell'ordine di grandezza di 1 o 2 giorni.

(1) E. FERMI, « Ricerca Scientifica », 5 (1) p. 283, p. 330 (1934).

iodine isotopes

used in nuclear medicine

Discovery of artificial radioactivity induced by slow neutrons

Discovery:	**Saturday**	**20.10.34**
First paper:	**Monday**	**22.10.34**
Patent:	**Friday**	**26.10.34**

O. D'Agostino E. Segrè

E. Amaldi F. Rasetti E. Fermi

1934

The patent to "increase the production of artificial radioactivity with neutron bombardment"

Discovery: Saturday 20 October (*)

Patent: Friday 26 October because of Orso Mario Corbino

"To obtain radioactive substances in quantities of practical importance"

(*) A. De Gregorio : not on October 22!

REGNO D'ITALIA

MINISTERO DELLE CORPORAZIONI

UFFICIO DELLA PROPRIETÀ INTELLETTUALE

Attestato di Privativa Industriale

№ 324458

Nel Registro degli attestati di privativa industriale di questo Ufficio è stata regolarmente inscritta la domanda depositata, coi documenti voluti dalla legge, all' Ufficio stesso *nel giorno* ventisei *del mese di* ottobre *1934 alle ore* 12,15 *da* Fermi Enrico, Amaldi Edoardo, D'Agostino Oscar, Pontecorvo Bruno, Rasetti Franco, Segrè Emilio e Trabacchi Giulio Cesare { a Roma

per ottenere una privativa industriale per il trovato designato col titolo:

Metodo per accrescere il rendimento dei procedimenti per la produzione di radioattività artificiali mediante il bombardamento con neutroni.

Il presente attestato non garantisce che il trovato abbia i caratteri voluti dalla legge perché la privativa sia valida ed efficace, e viene rilasciato senza esame preliminare del merito e della novità di esso

Roma, li -2 FEB 1935 Anno XIII

Il Direttore

Nei riferimenti al presente *attestato* richiamare *soltanto* il suindicato numero, adottando la dizione PRIVATIVA ITALIANA N. 324458

B

La Tipografica - Roma XII - Ord. 3543 - (5.000)

Fifty years later

"We were extremely pleased and amused, not so much because a patent could result in a financial benefit for the 'inventors', but rather because a work, carried out with great energy and dedication, only for its intrinsic merits, had unexpectedly brought us to applications which, in addition, would be mainly of a scientific and a medical nature"

E. Amaldi – Phys. Report 1984

The American patent was deposited on October 3, 1935

July 2, 1940. E. FERMI ET AL. 2,206,634

PROCESS FOR THE PRODUCTION OF RADIOACTIVE SUBSTANCES

Filed Oct. 3, 1935

Fig. 1.

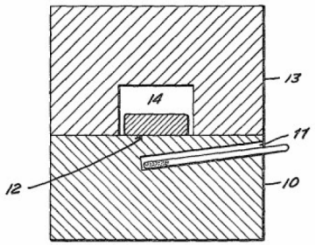
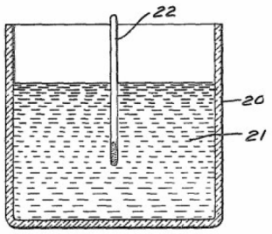


Fig. 2.



INVENTORS
ENRICO FERMI, EDOARDO AMALDI,
BRUNO PONTECORVO, FRANCO RASETTI, EMILIO SEGRE
BY
ATTORNEYS

Patented July 2, 1940 2,206,634

Uranium is explicitly quoted

UNITED STATES PATENT OFFICE

2,206,634

PROCESS FOR THE PRODUCTION OF RADIOACTIVE SUBSTANCES

Enrico Fermi, Edoardo Amaldi, Bruno Pontecorvo, Franco Rasetti, and Emilio Segrè, Rome, Italy, assignors to G. M. Giannini & Co., Inc., New York, N. Y., a corporation of New York

Application October 3, 1935, Serial No. 43,463
In Italy October 26, 1934

7 Claims. (Cl. 204—31)

This invention relates to the production of isotopes of elements from other isotopes of the same or different elements by reaction with neutrons, and especially to the production of artificial radio activity by formation of unstable isotopes.

It has been known for many years that, although each chemical element has always the same atomic number or charge, it may exist in different forms having different atomic weights. These forms of the elements are referred to as isotopes.

It has also been known that the radio-active elements, by disintegration or break down occurring in their nuclei are spontaneously converted into various isotopes of other elements. Thus, for example, the radio-active element uranium may be converted into lead of atomic weight 206, while the element thorium may be converted into a different isotope of atomic weight 208.

It has long been known that such spontaneous used which require tremendous energy to break through the potential barrier surrounding the nucleus; and that if, instead of charged particles, neutrons are used for the nuclear reactions, the greatest efficiencies are in some cases attained with low energy or "slow" neutrons, e. g., of the order of a few hundred electron volts, or even much less down to a small fraction of an electron volt.

Neutrons when produced in any ordinary manner, e. g., by the action of radon on beryllium or of polonium on beryllium or by bombardment of atomic nuclei with artificially accelerated particles, might have a very wide range of energies but high average energy. These energies range up to several million volts. It is necessary, therefore, if the greatest efficiency of reaction is to be attained, to reduce by artificial means the energy of these neutrons. We describe below a method for slowing down fast neutrons.

Some dates (Simone Turchetti)

American Patent:	3 October 35 2 July 40	Gabriello Giannini & Co. patent is granted
Request to the military patent office of ORSD	14 June 46	Giannini and L. Bernard 0.45 M$
Request to the civil patent office of USAEC	13 October 48	Giannini and L. Bernard 1,9 M$

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Request to the civil patent office of USAEC	13 October 48	Giannini and L. Bernard 1,9 M$
Trial against Government	15 August 50	Giannini and L. Bernard 10 M$
Pontecorvo disappears	1 September 50	

November 52 : each inventor receives 28,000$

Interview to Piero Angela

“ With Ginestra we immediately agreed. ‘Such an amount of money would create problems to us. Our existence would be destroyed. We would eventually change life and this we do not want.’

We took a decision: we would take only a small fraction of the money and we would use the rest for the construction of an Italian cyclotron.”

Domenico Marotta, Director of Istituto di Sanitá (1946) and the Queen Maria Josè of Savoia

Visits to the States in 1935 and 1936

To obtain information on accelerators

1935: Rasetti went to Pasadena and Berkeley

1936: Segrè went to Berkeley (27-inch cyclotron)

Amaldi went to Columbia and Carnegie Mellon

"Probleme der Atomkernphysik" in Copenhagen
June 1936: Bohr's compound nucleus

Bohr Rosenfeld Amaldi Wick

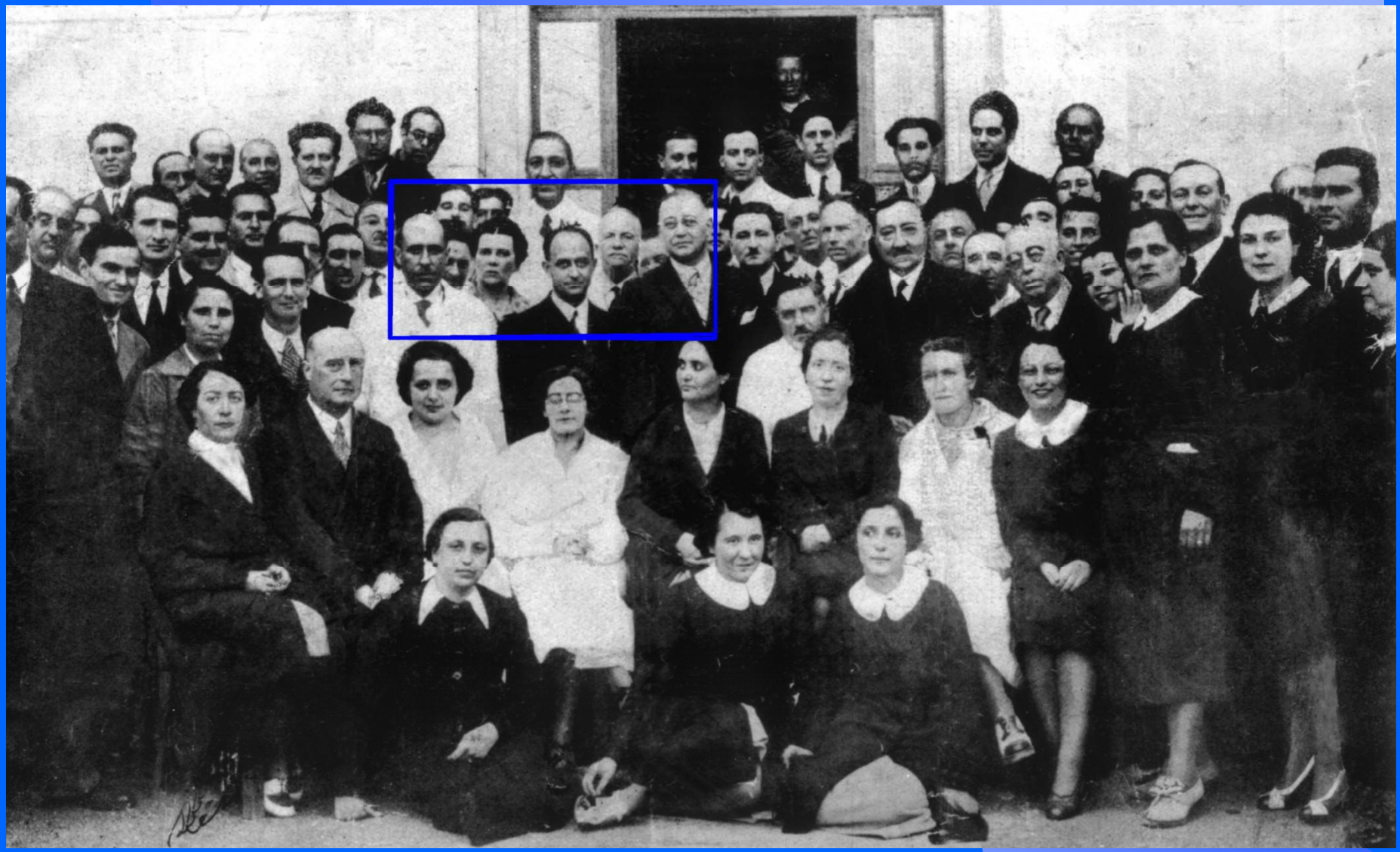
Pauli Jordan Heisenberg Born Meitner Stern Franck

Letter by D. Marotta to E. Fermi – 16.11.36

I nuovi orizzonti che ha aperto per la terapia dei tumori maligni la possibilità di fabbricare sostanze radioattive artificiali in quantità considerevoli mi fa pensare alla convenienza che l'Istituto di Sanità faccia il possibile per organizzare i mezzi tecnici per tali preparazioni. Prima però di prendere in considerazione il progetto proposto dal Capo del Labratorio di Fisica di questo Istituto desidererei avere il parere di Vostra Eccellenza.

The new vistas opened for tumour therapy by the possibility of producing large quantities of radioactive substances convince me that it is convenient for 'Istituto di Sanità' to procure the technical means for such productions. However , before considering the project proposed by the Chief of the Physics Laboratory (G. C. Trabacchi), I would like to have the opinion of Your Excellency.

Lecture by Enrico Fermi at Istituto di Sanità Pubblica 29 .5.1938



G.C. TRABACCHI – E.FERMI – D.MAROTTA

Lecture by Enrico Fermi at Istituto di Sanità Pubblica 29 .5.1938

PROSPETTIVE DI APPLICAZIONE DELLA RADIOATTIVITÀ ARTIFICIALE

"It can be forseen WITHOUT DOUBTS that the (new) radioactive substances will find THERAPEUTICAL APPLICATIONS similar to the one of natural occurring radioactive substances.

Moreover and independently, the use of large quantities of radioactive substances will open, I HOPE, the way to many interesting studies in biology and chemistry through the use of radioelements as 'INDICATORS' "

È da prevedere senz'altro che le sostanze radioattive artificiali troveranno un impiego terapeutico analogo a quello delle sostanze radioattive naturale.

Ma anche indipendentemente da queste possibilità, l'uso delle sostanze radioattive artificiali in quantità rilevanti renderà possibili, io spero, anche molte interessanti ricerche nel campo della biologia e della chimica, usando i radioelementi come " indicatori".

The “tube” was built on the last floor of Istituto di Sanità

The 1 MeV Cockcroft-Walton

Fotografia d'insieme dell'impianto a 1 milione di volt per la accelerazione di ioni dell'Istituto Superiore di Sanità (Laboratorio Fisico) in Roma.

Built by

Ageno, Amaldi,

Bocciarelli, Trabacchi

after Fermi left Italy in 1938

Mario Ageno

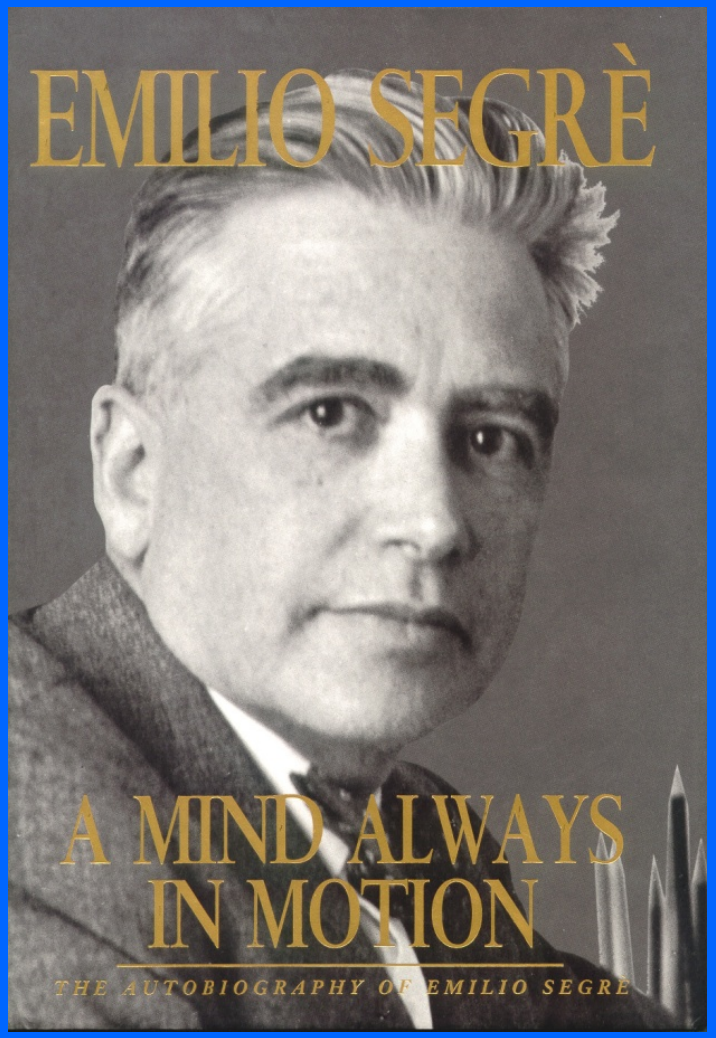
During the II World War: First test of the optical theorem

In the Aula of Istituto Superiore di Sanità

Figure 3. *Amaldi, Rasetti, and Segrè in their old age. Courtesy of AIP Emilio Segrè Visual Archives.*

The medical applications of slow neutrons

Radioactivity in diagnostics:
SPECT = Single Photon Emission Computer Tomography

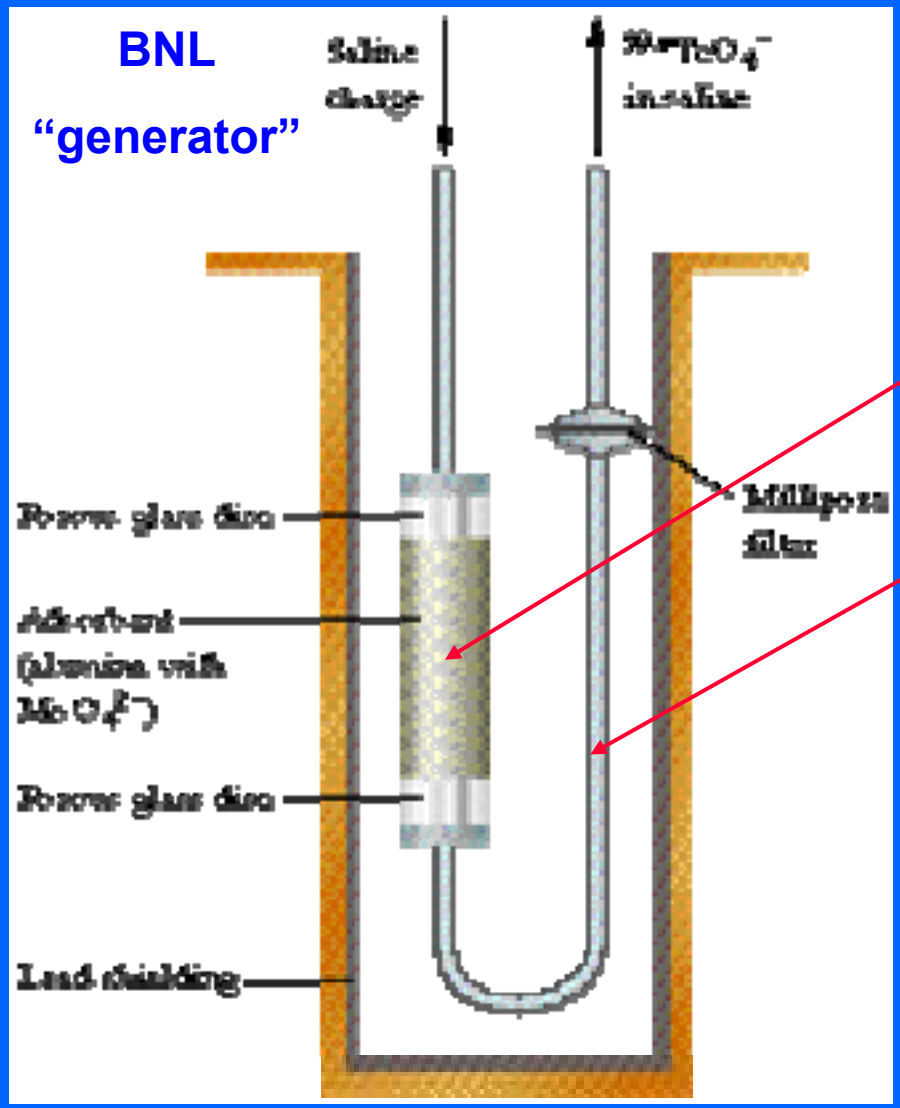


Emilio Segrè

1936: Discovery of technetium with Perrier

1938: discovery of ^{99m}Tc with McMillan

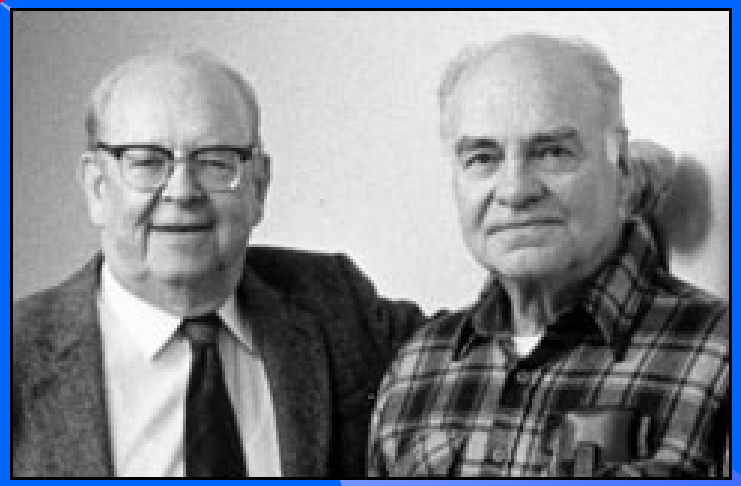
At BNL the « cow » was made productive



In reactors <u>slow neutrons</u> produce

$^{98}Mo + n = {}^{99}Mo + \gamma$

^{99}Mo (66 h) = ^{99m}Tc (6 h) + e^- + ν



Walter Tucker and Powell Richards

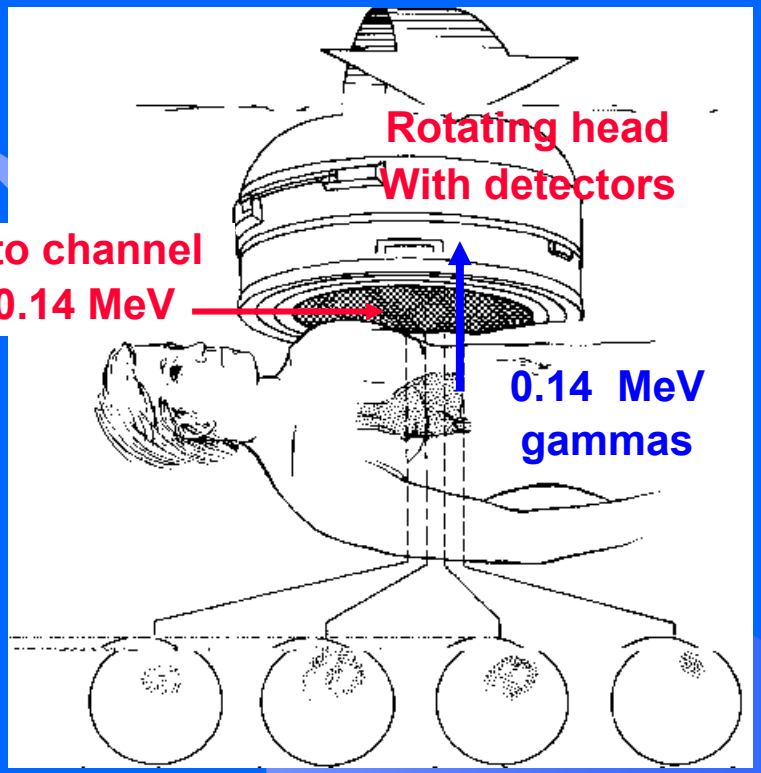
SPECT scanner

85% of all nuclear medicine examinations use technetium produced by slow neutrons in reactors

… liver

lungs

bones ……



Radioactivity in therapy: Cobalt-60 gammas spare the skin

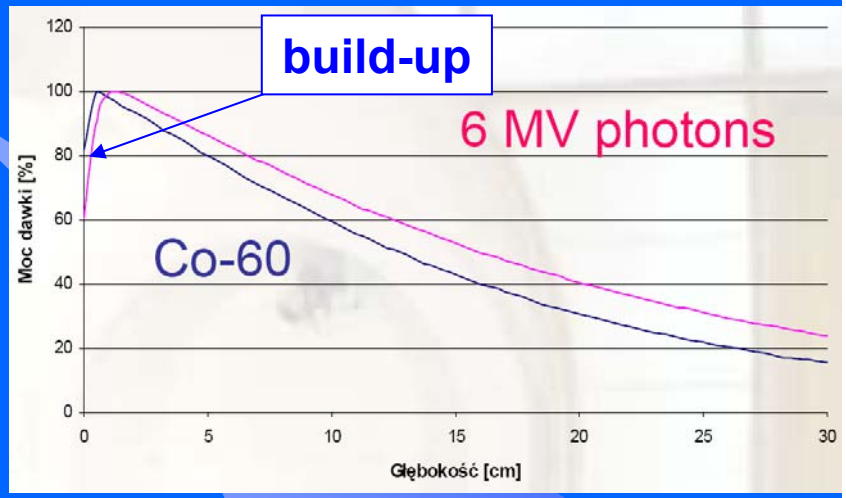
1943 - Bruno Pontecorvo joins the CANDU construction in Canada

1951 – first treatment at Victoria Hospital, London, Ontario

Roy Errington

founder of MDS Nordion

Dr. Ivan Smith

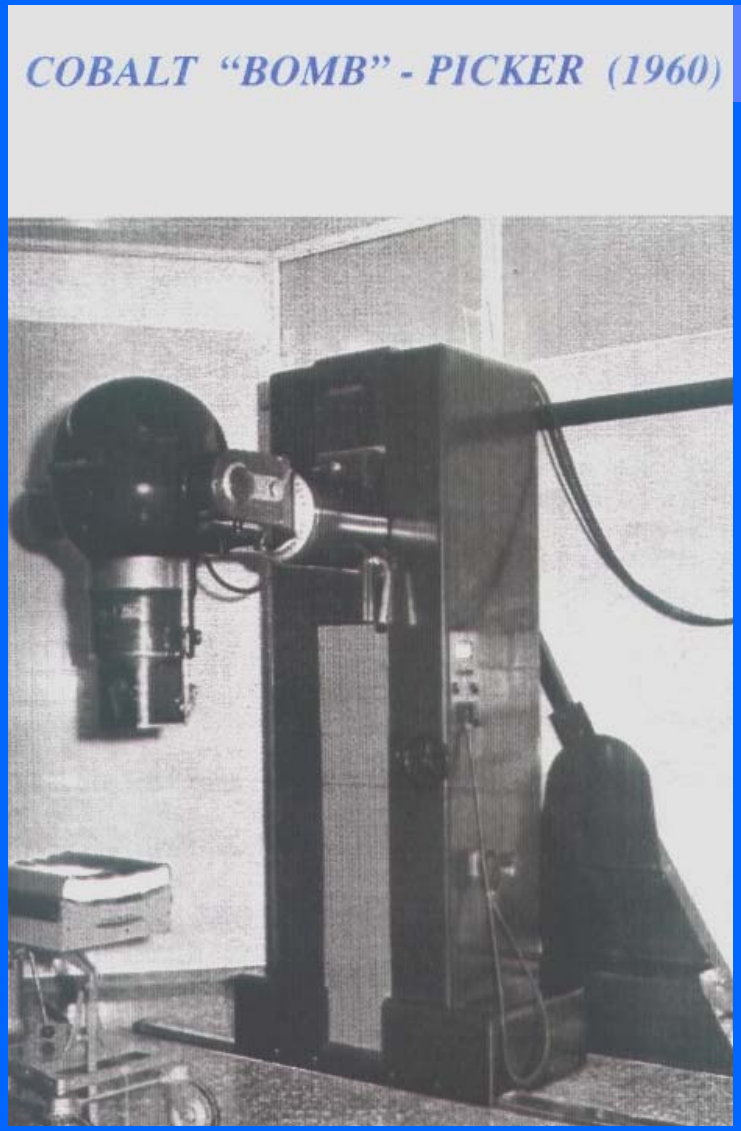


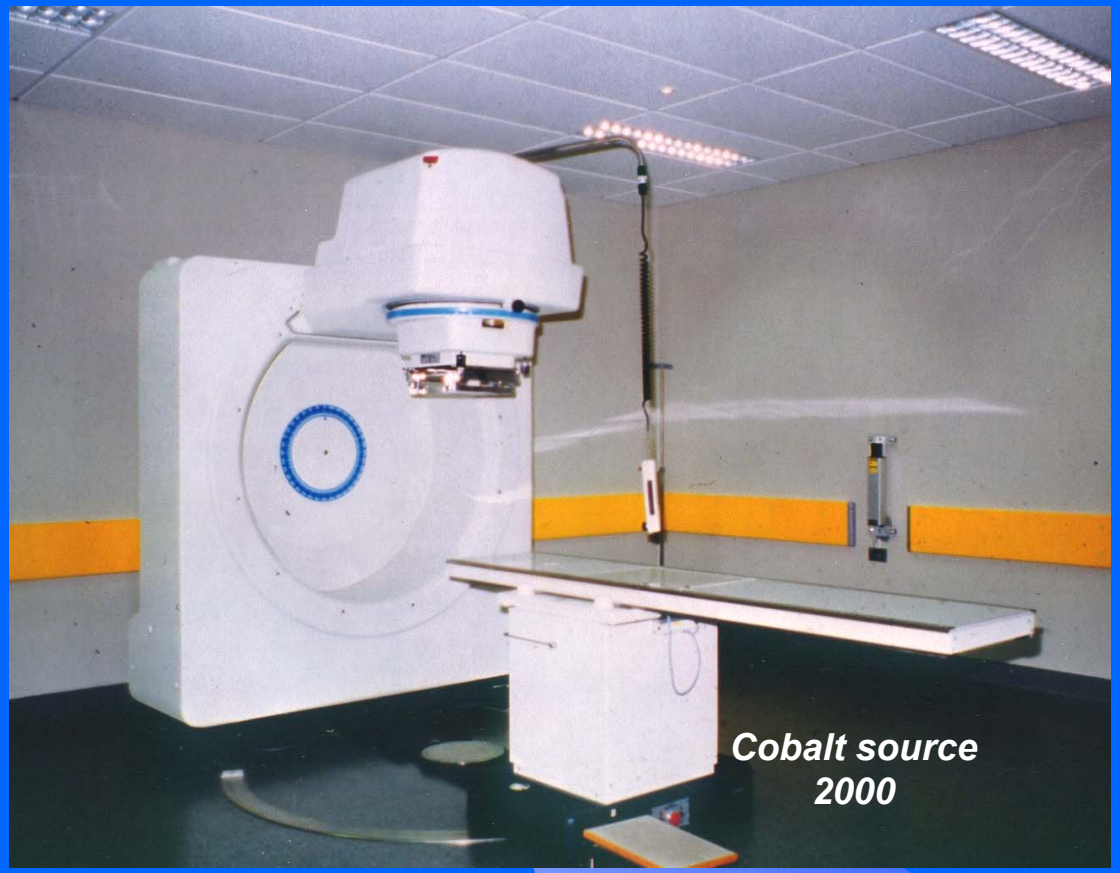
Cobalt-60 (1.1 MeV gammas)

has been produced for 50 years in CANDU reactors

by <u>slow neutrons:</u> today there is a problem

Old and new 'cobalt bombs'

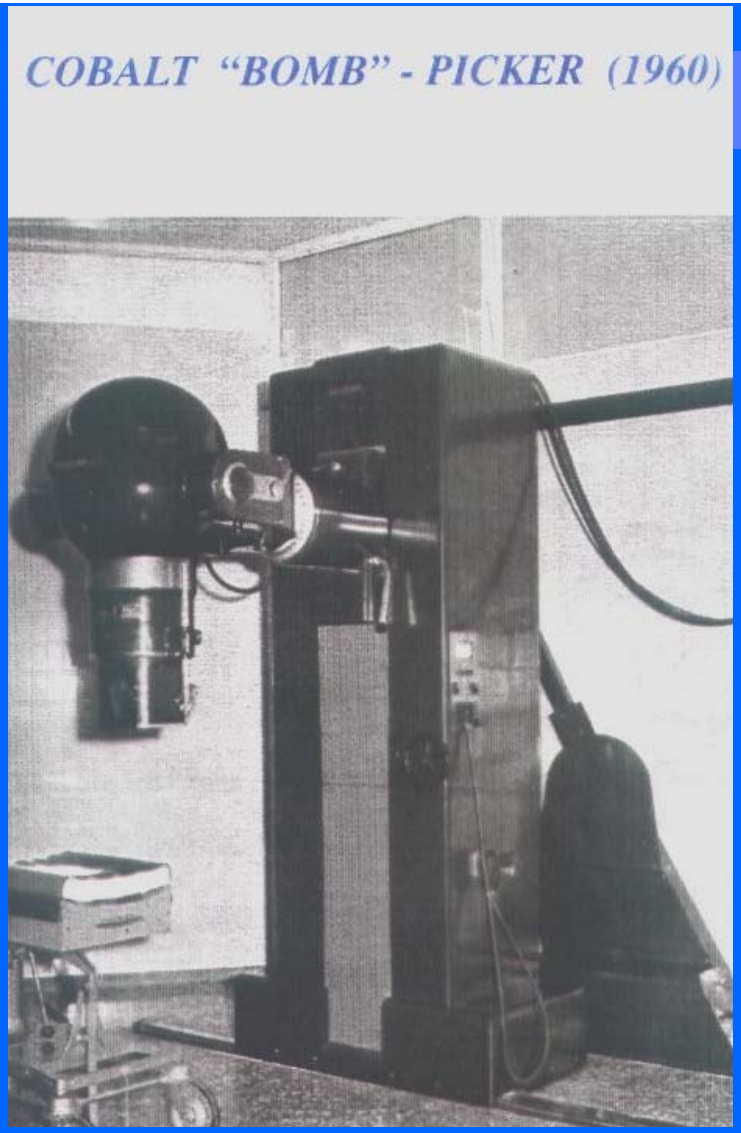


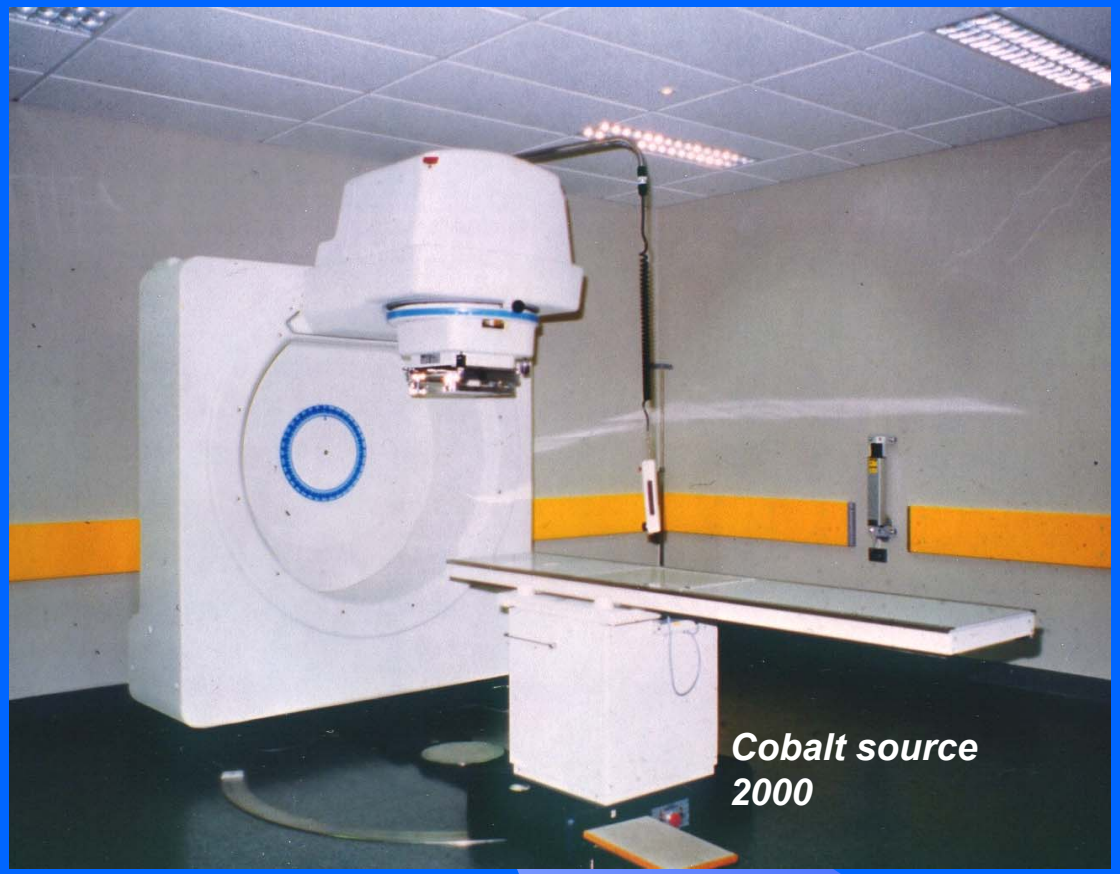


10 million patients treated with cobalt gamma rays

Important for developing countries

Radioactivity in cancer teletherapy





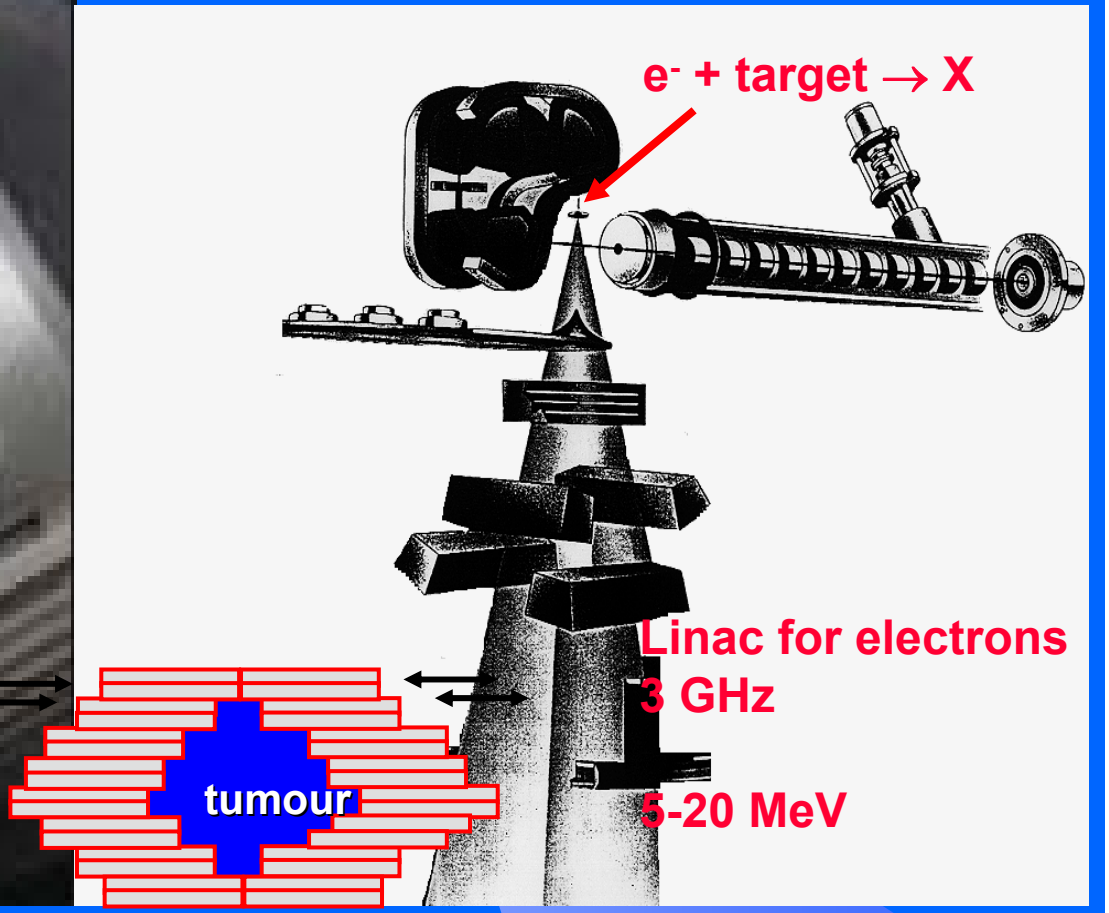
Cobalt-60 (1 MeV gammas)

has been produced for 50 years in reactors

by slow neutrons

The frontiers of radiotherapy

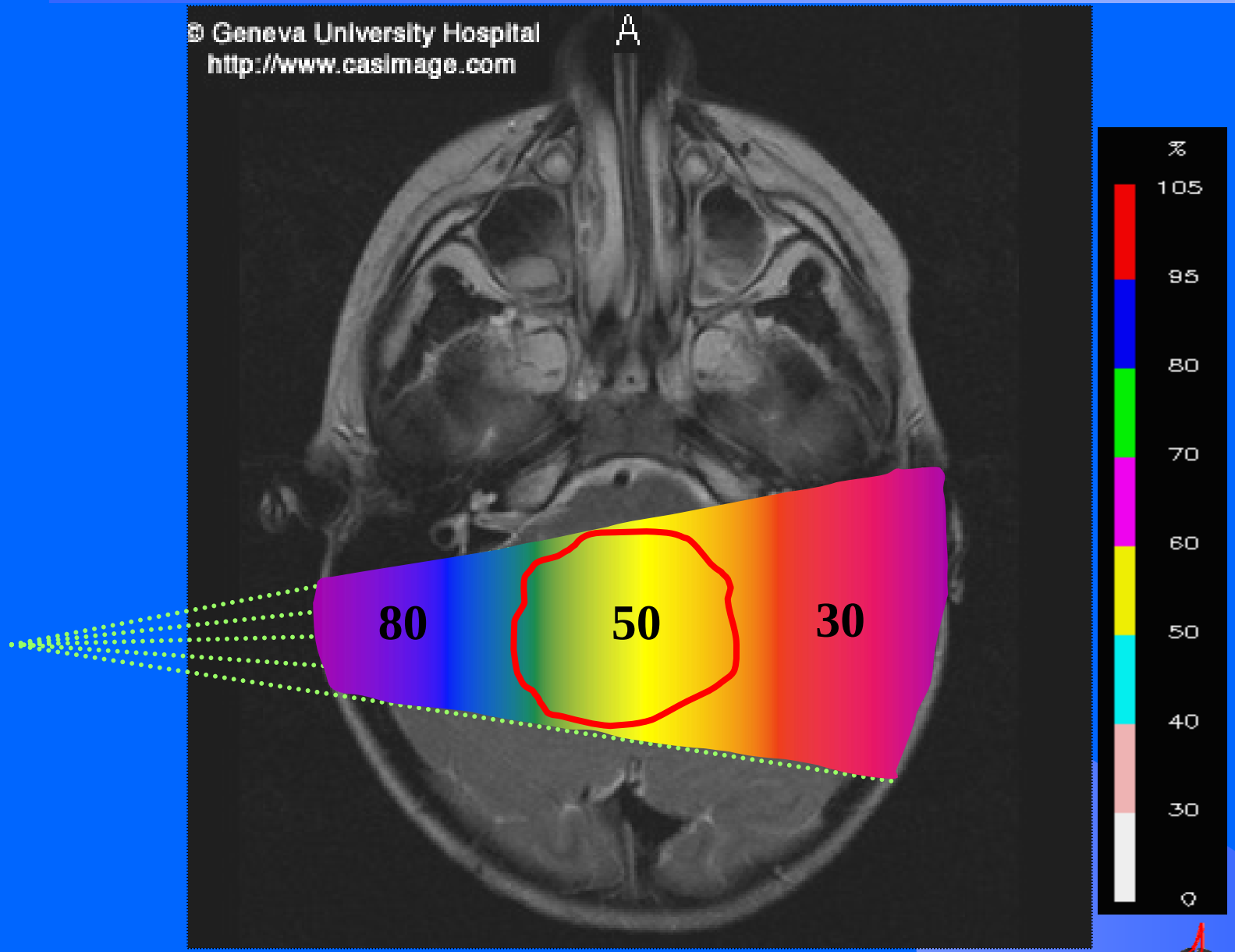
'Conventional' radiotherapy: linear accelerators dominate



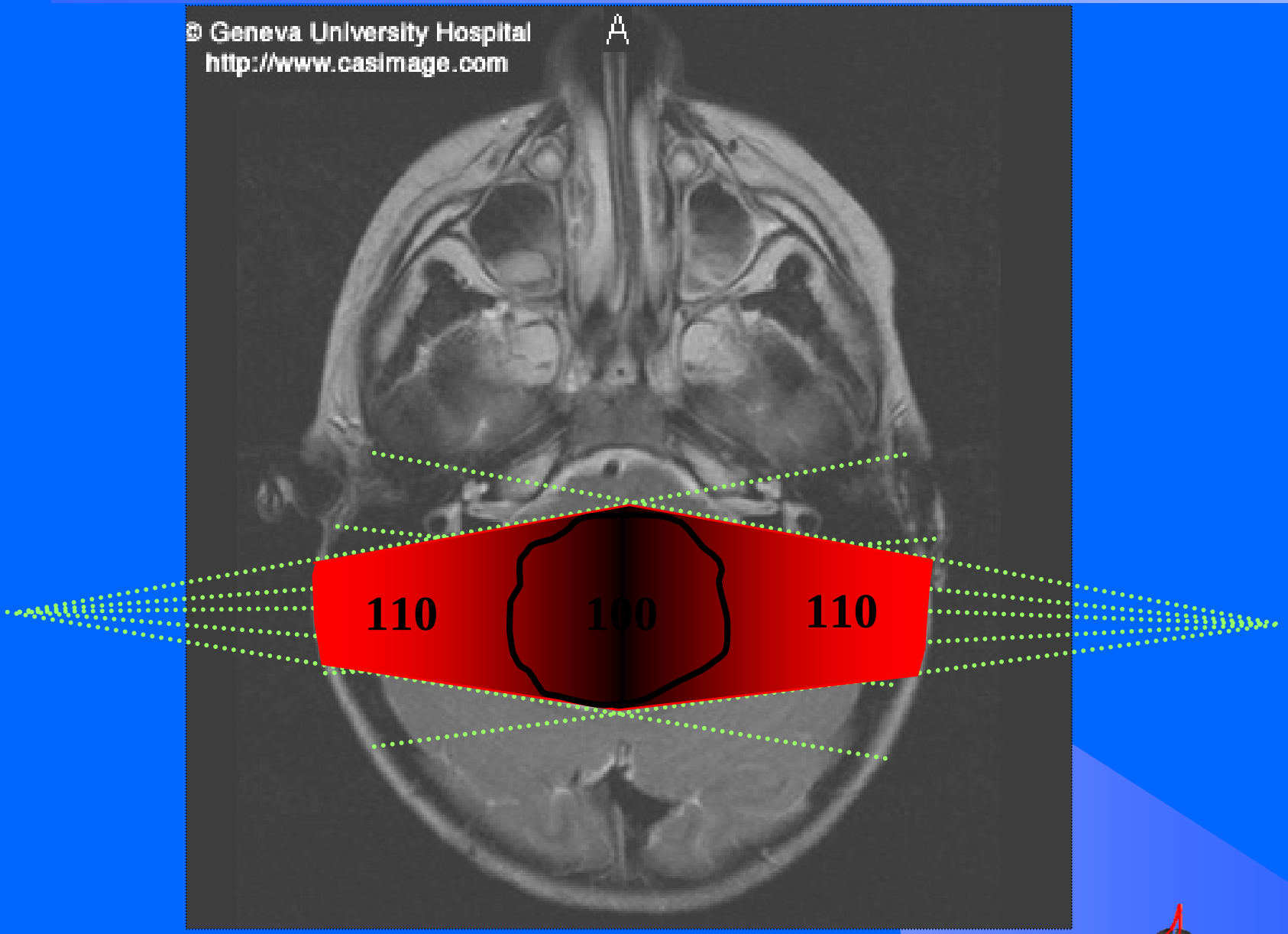
In the world radiation oncologists use 10 000 electron linacs

40% of all the existing accelerators of > 1 MeV

Two opposite photon beams

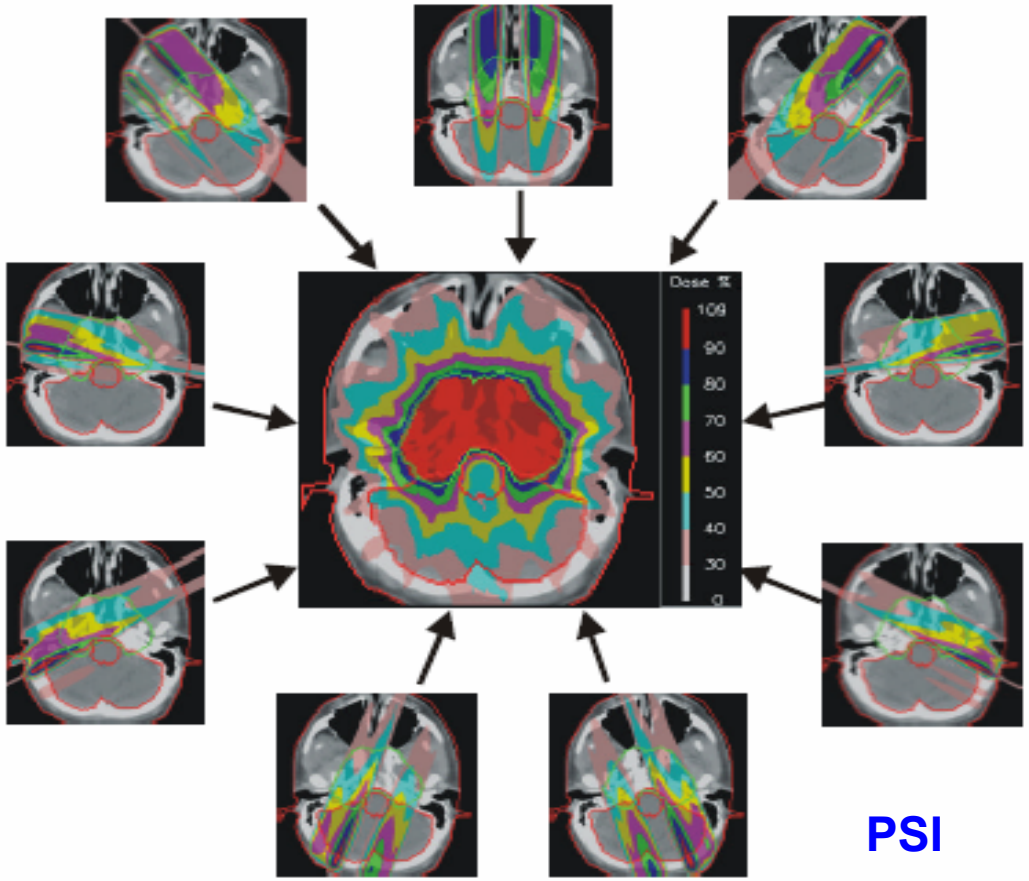


Two opposite photon beams



IMRT = Intensity Modulated Radiation Therapy with photons

9 NON-UNIFORM FIELDS



PSI

60-70 grays given typically in 30 fractions to allow healthy tissues to repair

The beginnings of hadrontherapy : 1943 - 1946

In 1943 the 1937 Harvard cyclotron was requested for war purposes.

H. Friendell: **“It is needed for medical purposes”**

P. Bridgeman: **“If you are going to use it for what I think you're going to use it for, you are welcome to take it".**

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In 1945 Robert Rathbun Wilson was asked by Lawrence to design a new 160 MeV cyclotron. After measuring the energy losses, he proposed radiotherapy wit protons (and carbon ions...)

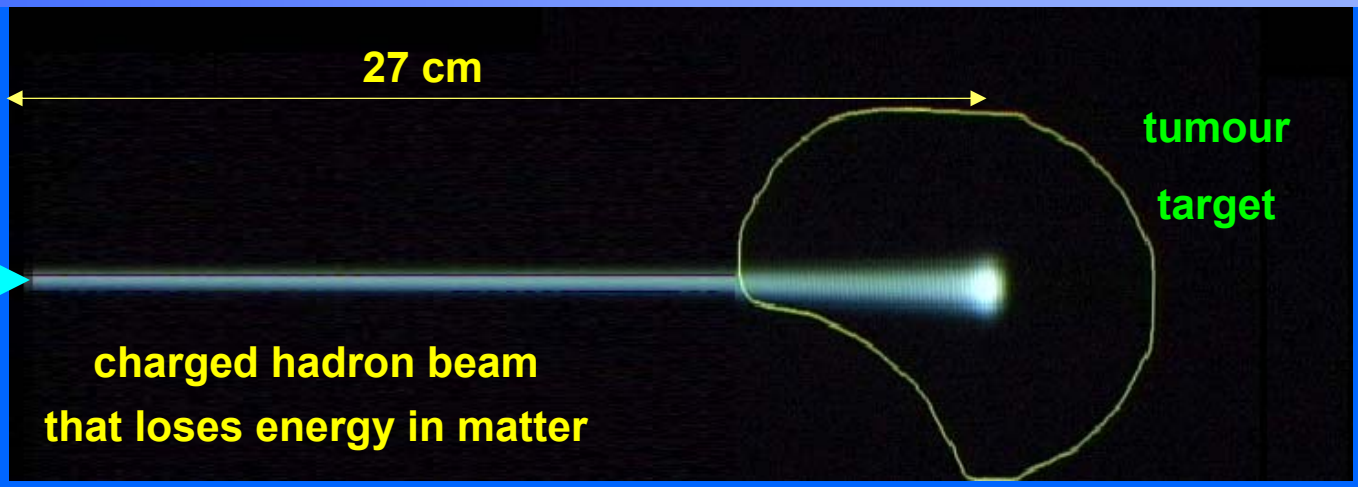
Hymer Friendell Bob Wilson Percy Bridgeman

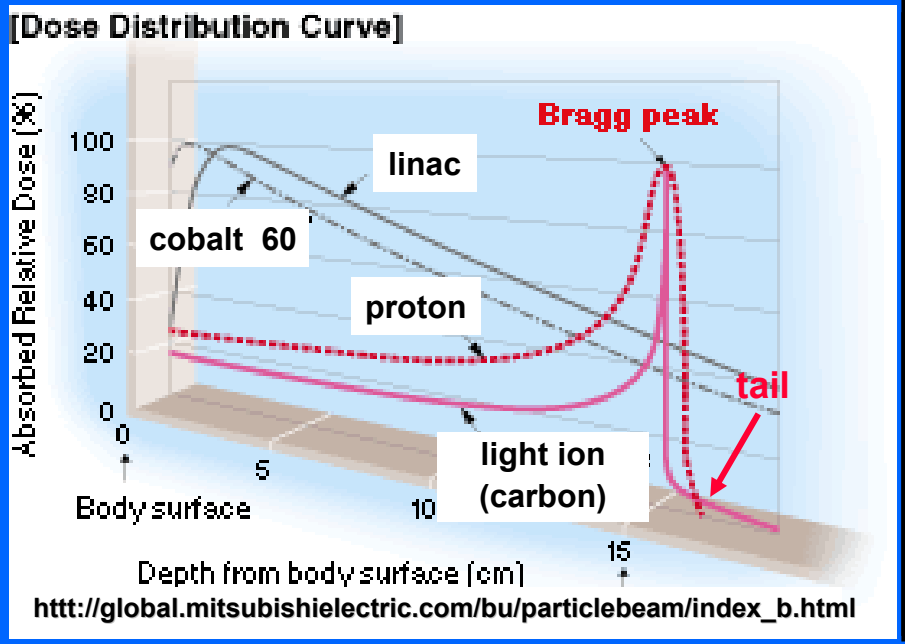
Protons and ions spare healthy tissues

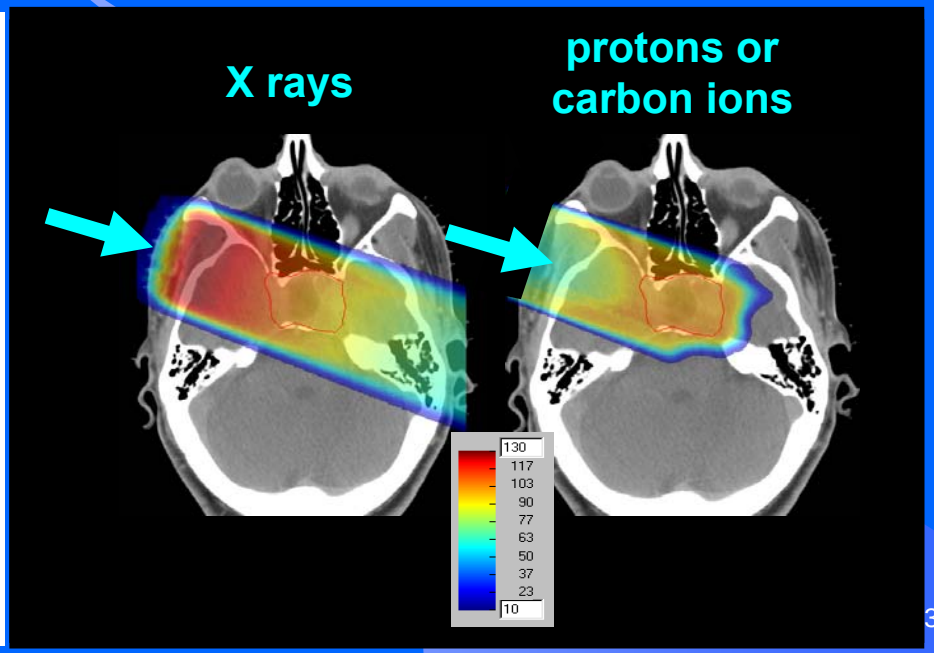
200 MeV - 1 nA protons

4800 MeV – 0.1 nA carbon ions

which can control radioresistant tumours

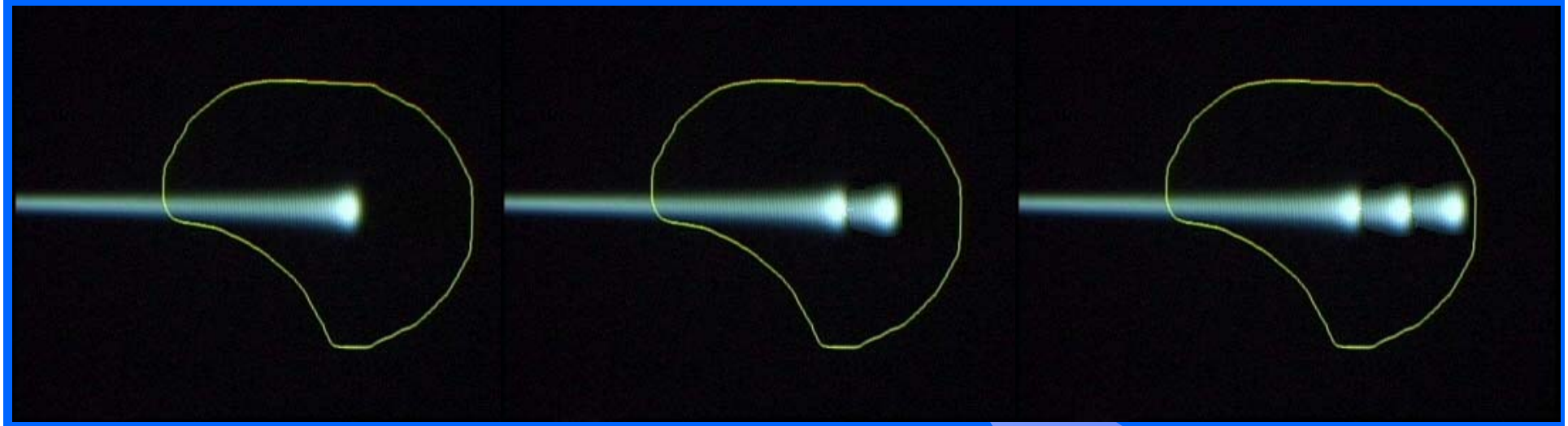






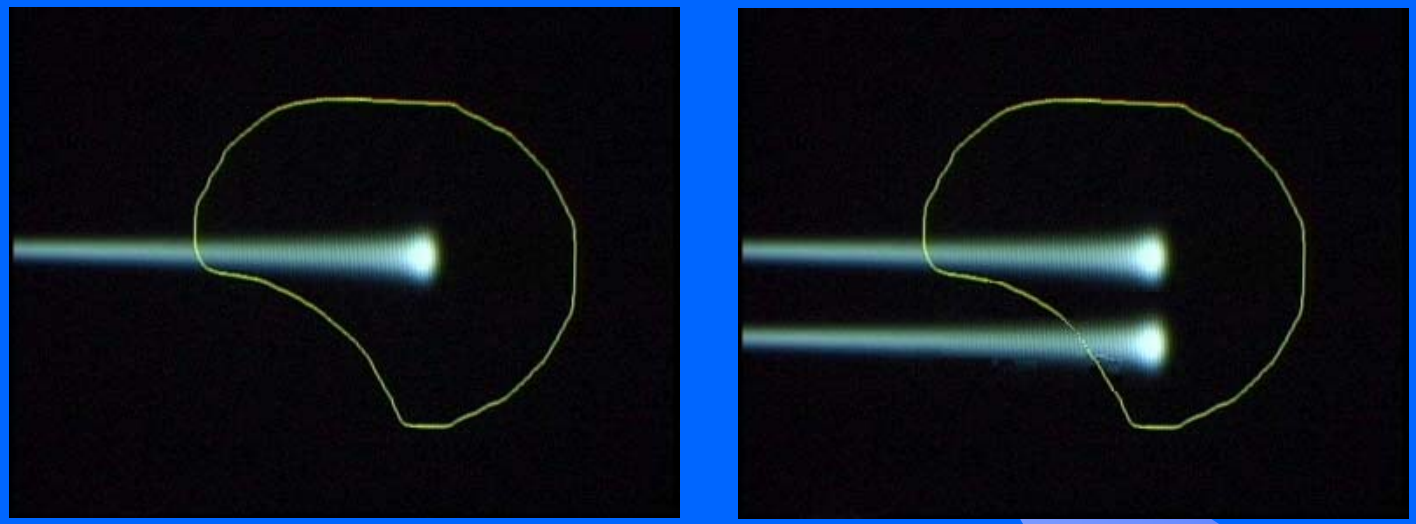
Charged hadrons can deliver the dose in three dimensions

Longitudinal mouvement by varying the energy of the beam

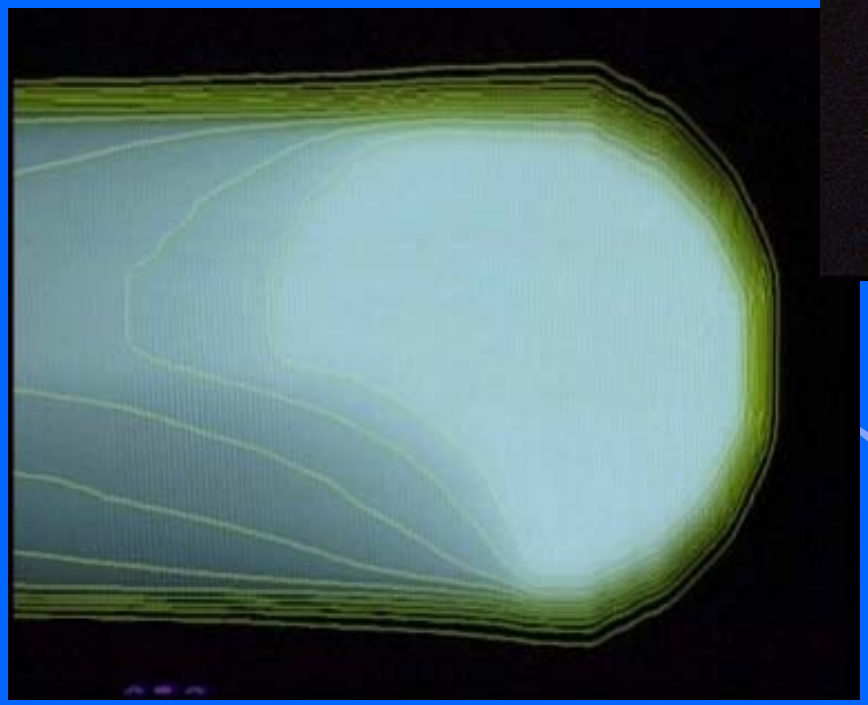


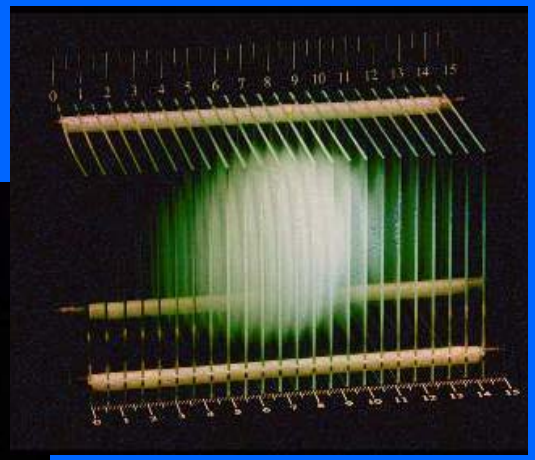
Charged hadrons can deliver the dose in three dimensions

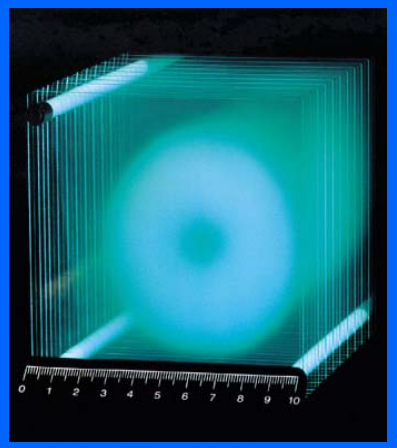
Lateral movement with a transverse magnetic field



Conformal distribution of the dose

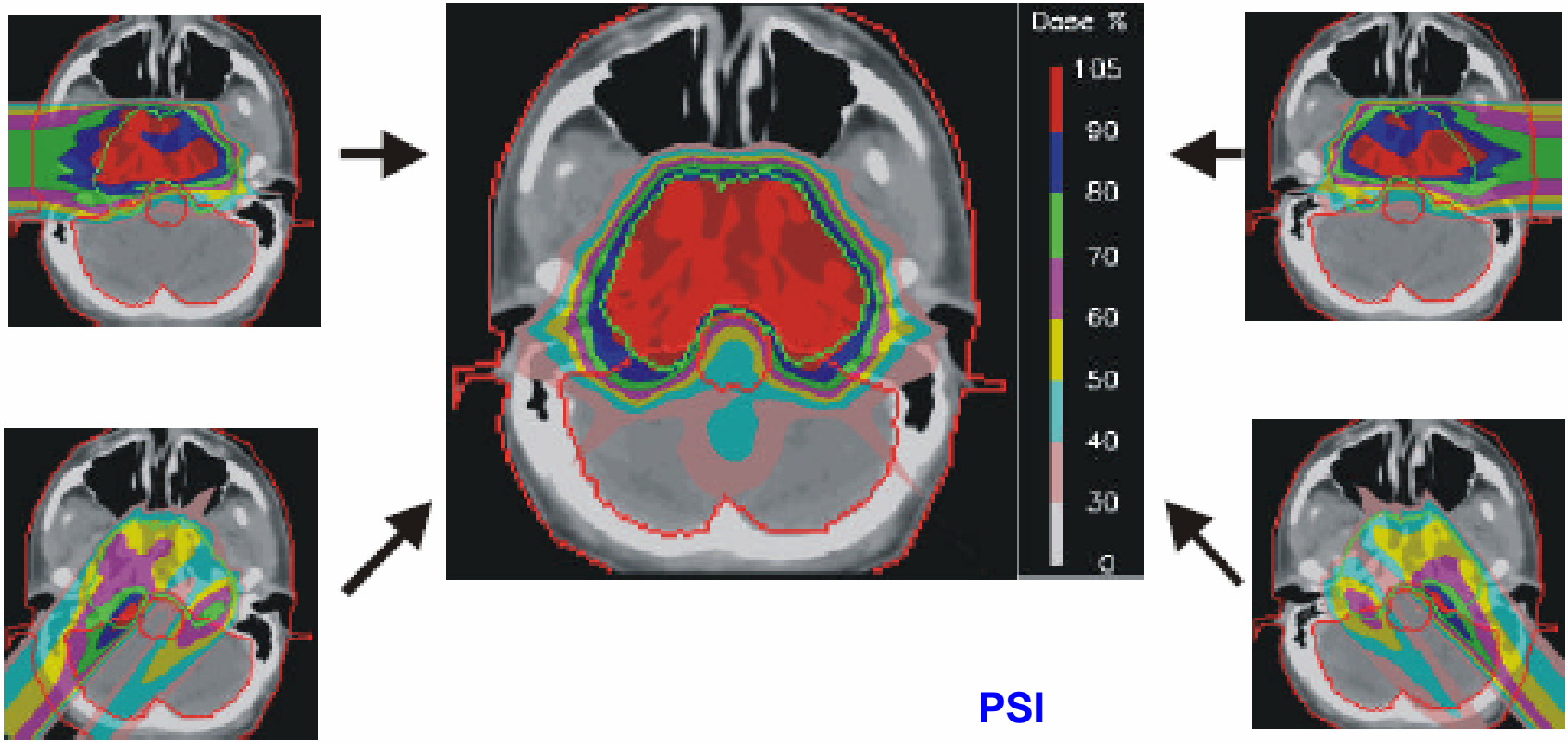






IMPT = Intensity Modulated Particle Therapy with protons

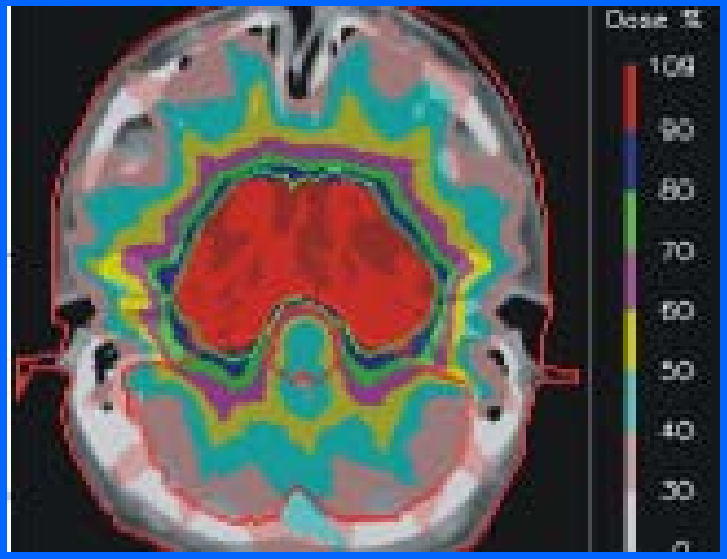
4 NON-UNIFORM FIELDS



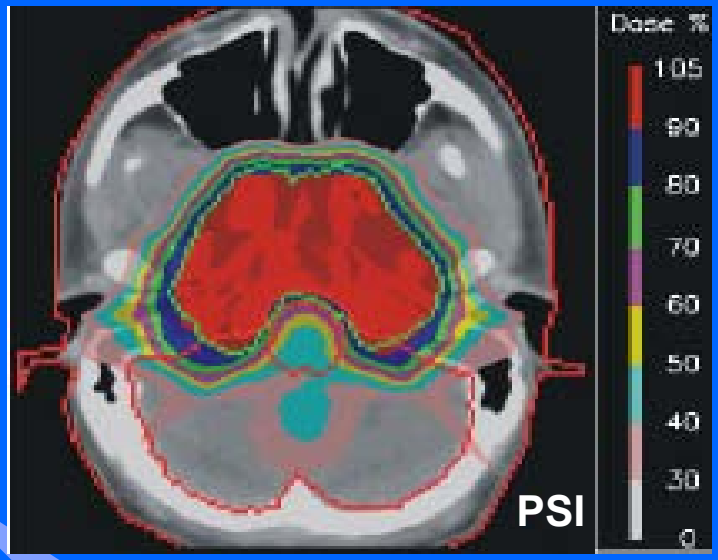
PSI

Protons are quantitatively different from X-rays

9 X-ray fields

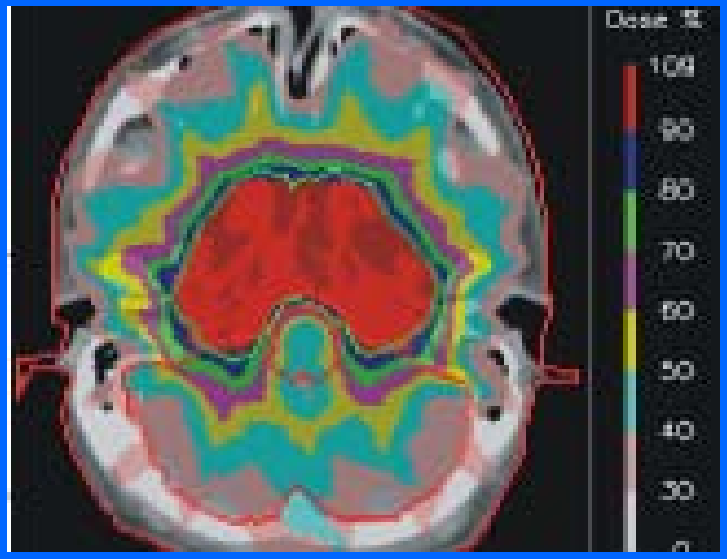


4 proton fields

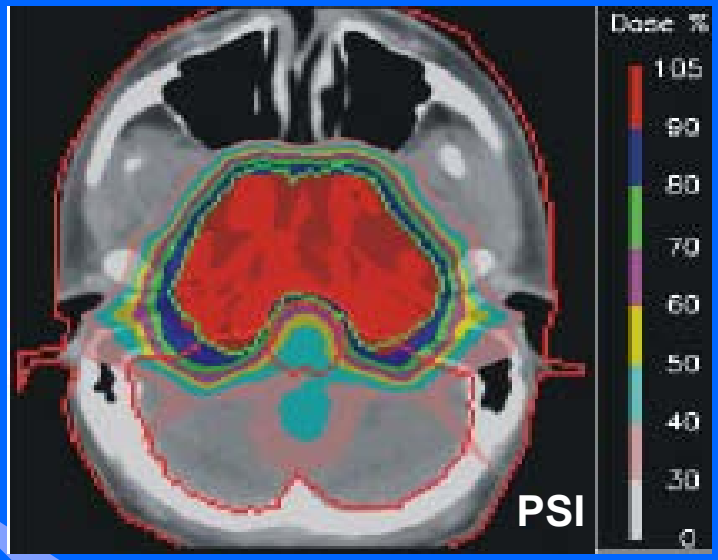


Carbon ions are qualitatively different from X-rays

9 X-ray fields



4 proton fields



Carbon ions deposit in a cell 24 times more energy than a proton producing not reparable multiple close-by double strand breaks

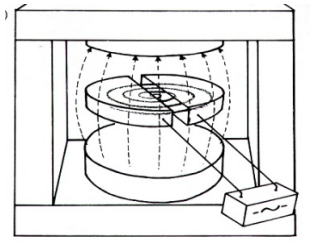
Carbon ions can control radio-resistant tumours

Accelerator based centres

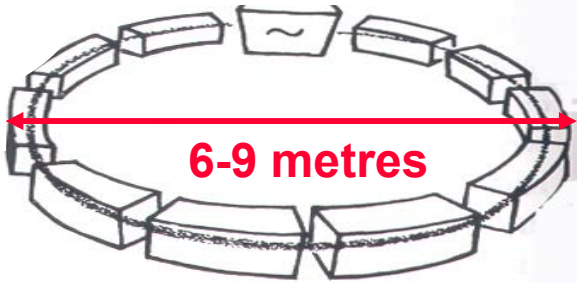
The accelerators used today in hadrontherapy are "circular"

Teletherapy with protons (200-250 MeV)

CYCLOTRONS (*) (Normal or SC)



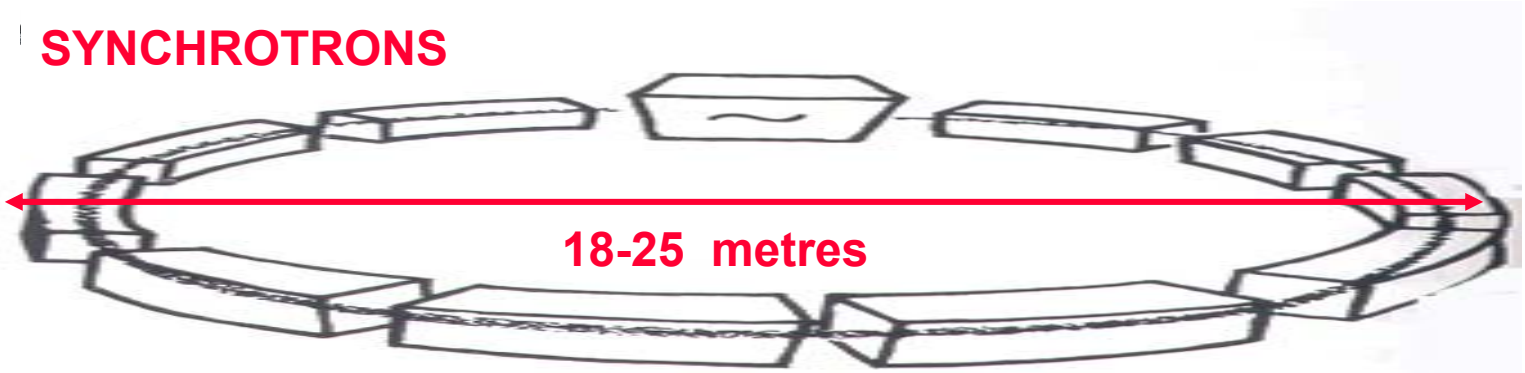
SYNCHROTRONS



(*) also synchrocyclotrons

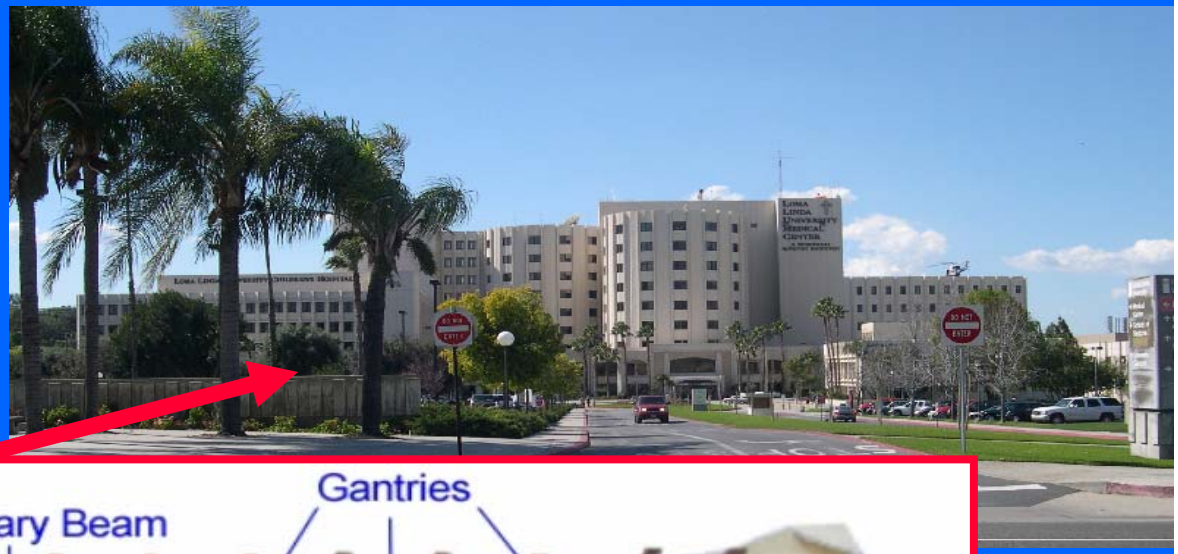
Teletherapy with carbon ions (4800 MeV = 400 MeV/u)

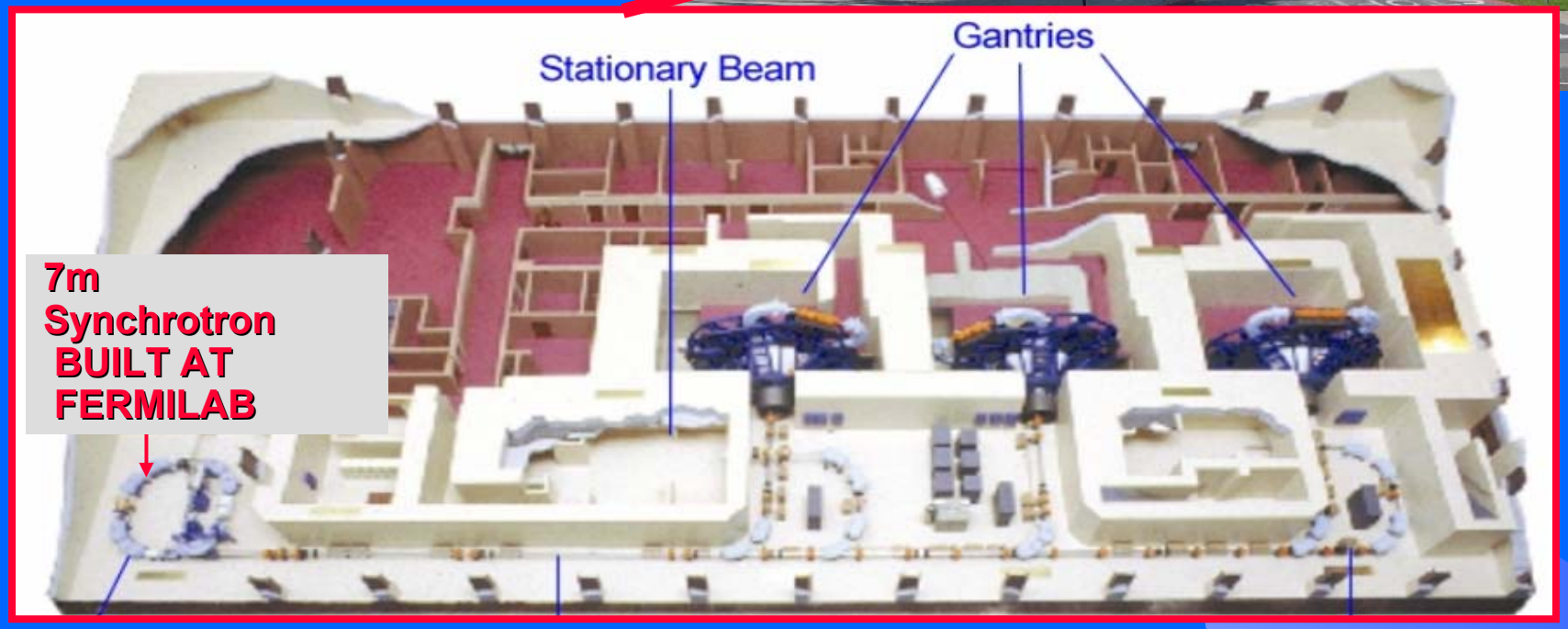
SYNCHROTRONS



Loma Linda Univesity Center: first patient in 1992

- First hospital-based proton-therapy centre
- 2008:170 sessions/day

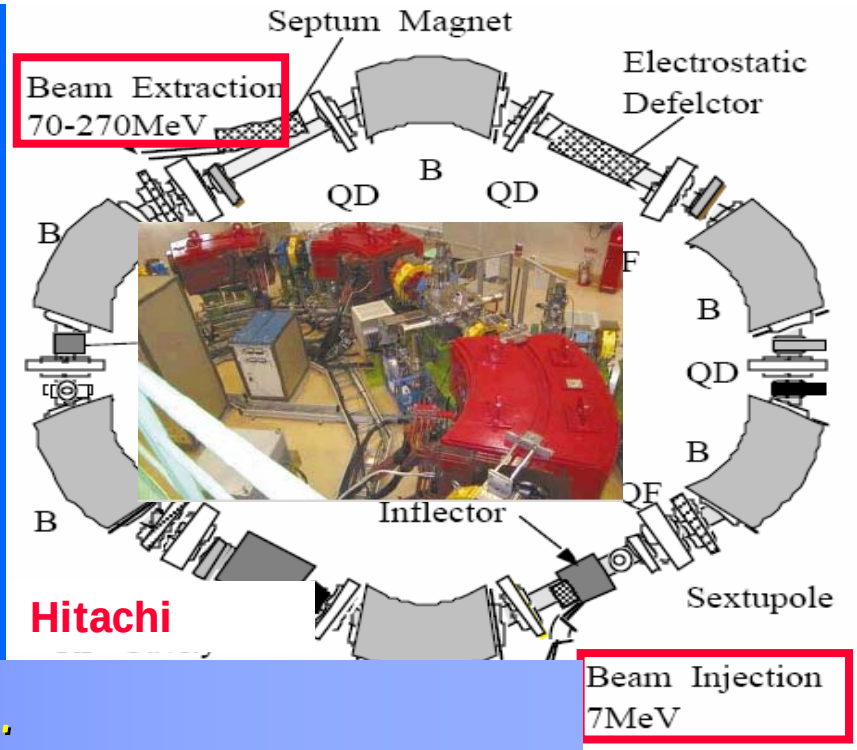




Cyclotron solution for protons by IBA - Belgium

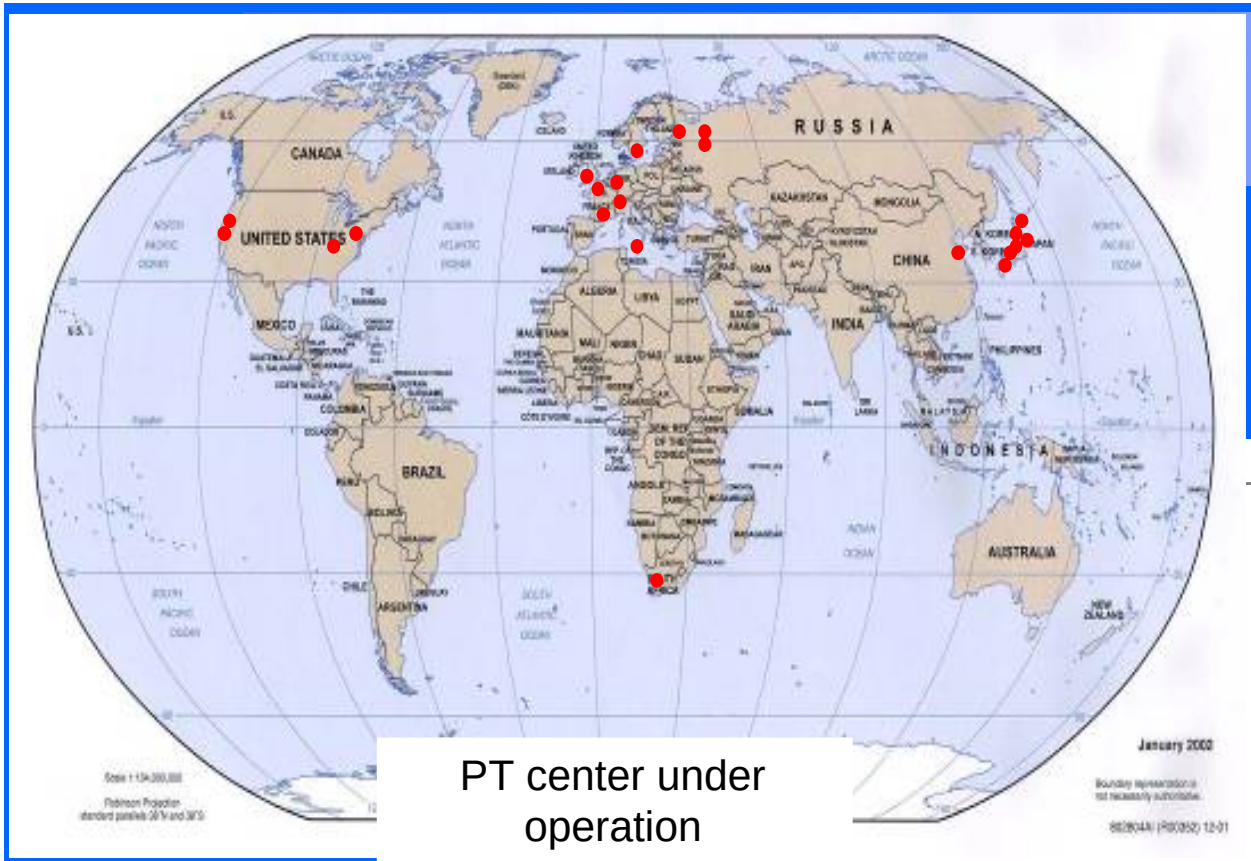
Five companies offer turn-key centres for 100 M€.

If proton accelerators were ‘small’ and ‘cheap’, no radiotherapist would use X rays.

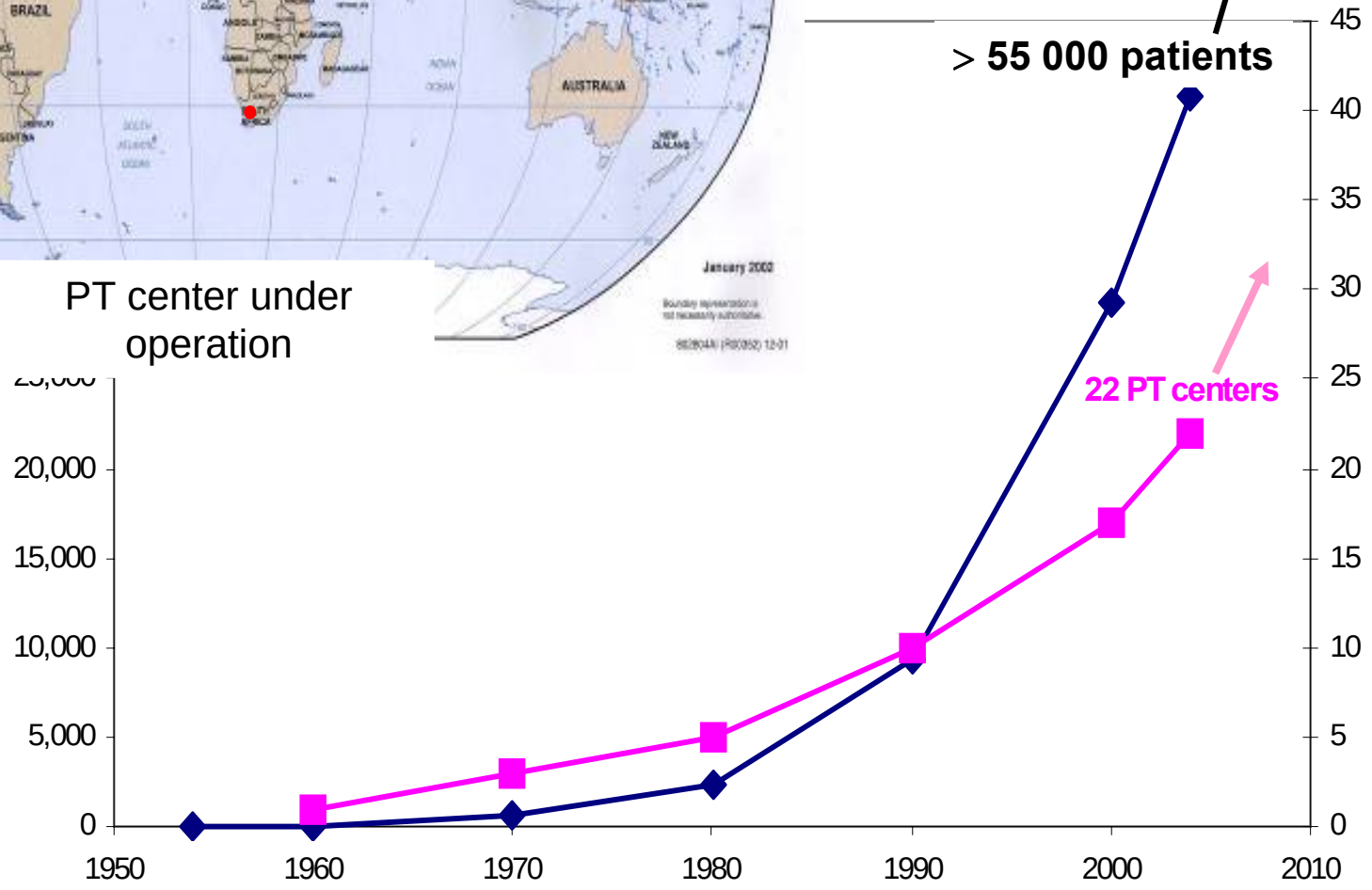


Protontherapy: a mature market…

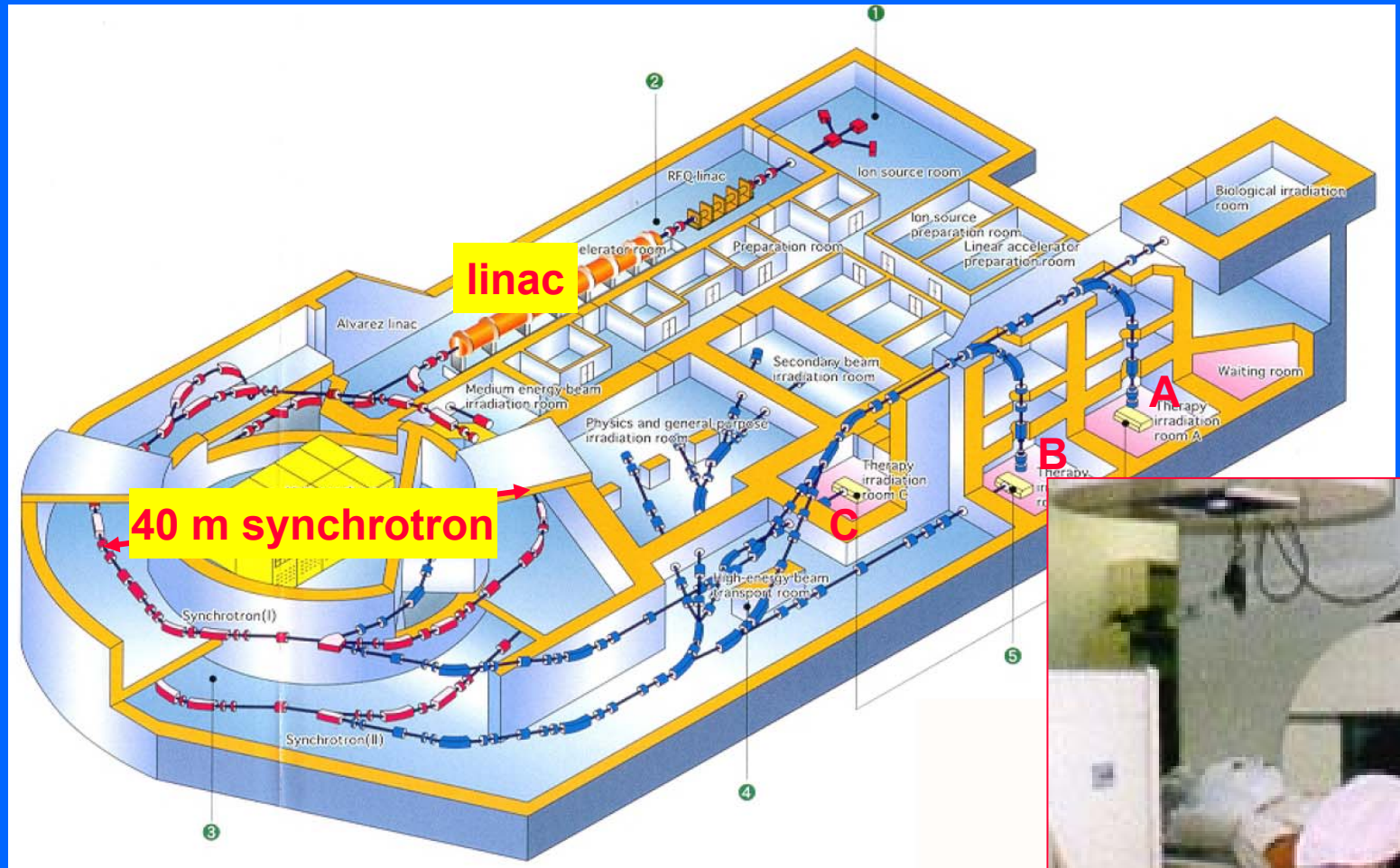
Protontherapy is booming



PT center under operation



HIMAC (Japan) pioneer in carbon therapy (Prof H. Tsujii)



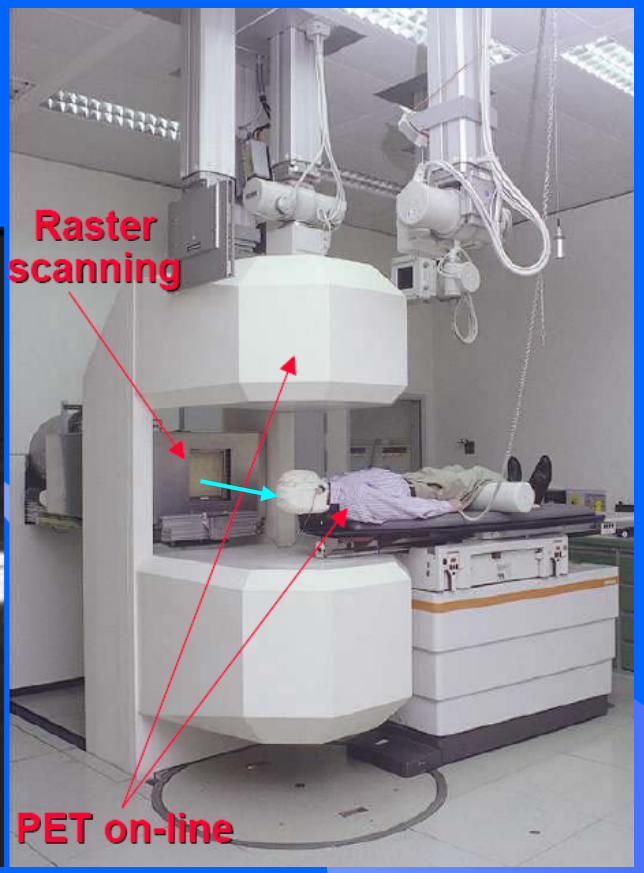
4000 patients

No repair mechanism: 6-9 sessions only

The Darmstadt GSI 'pilot project' (1997-2008)

Gerhard Kraft

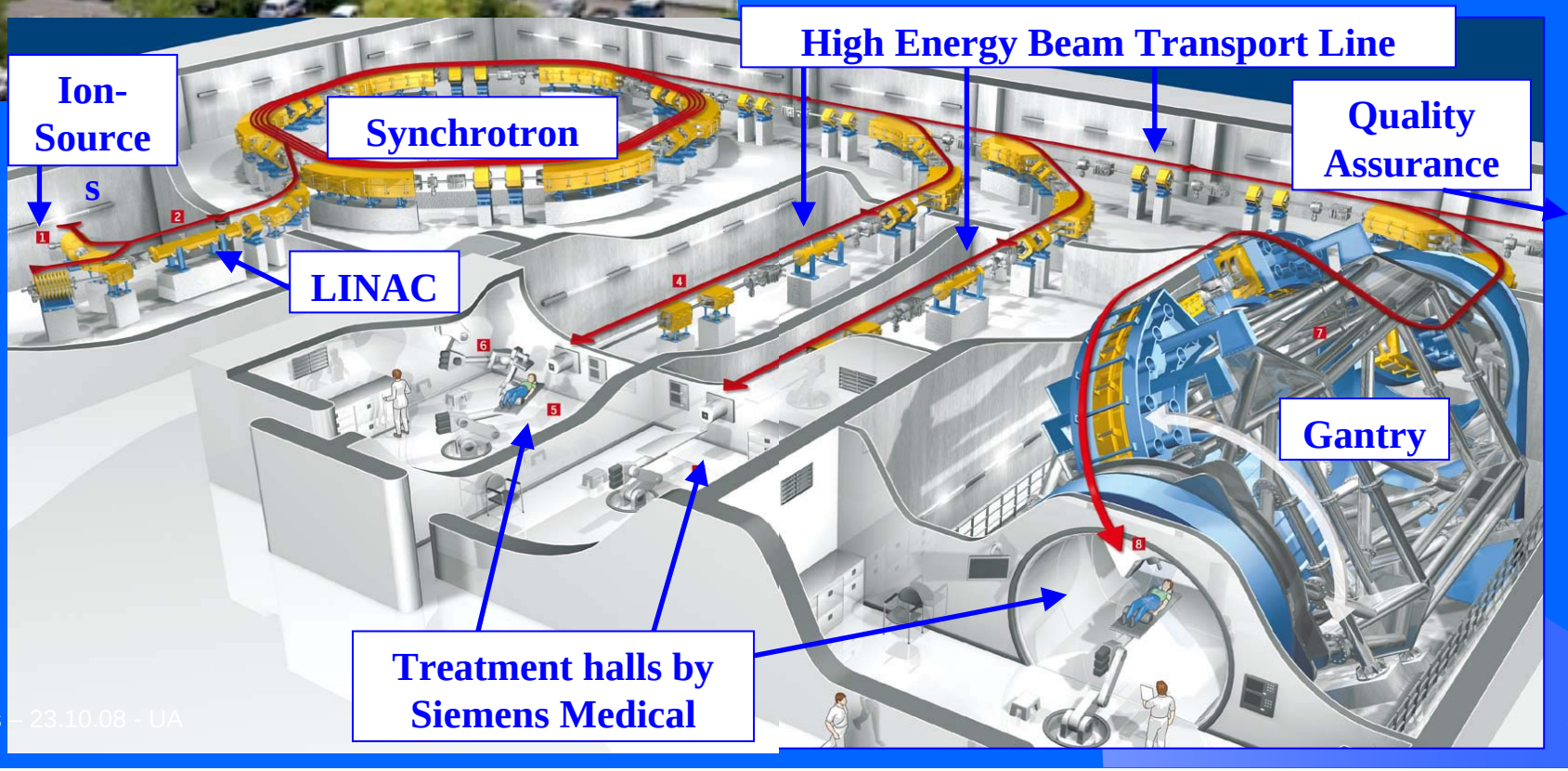
450 patients treated
with carbon ions
J. Debus (Heidelberg Univ.)



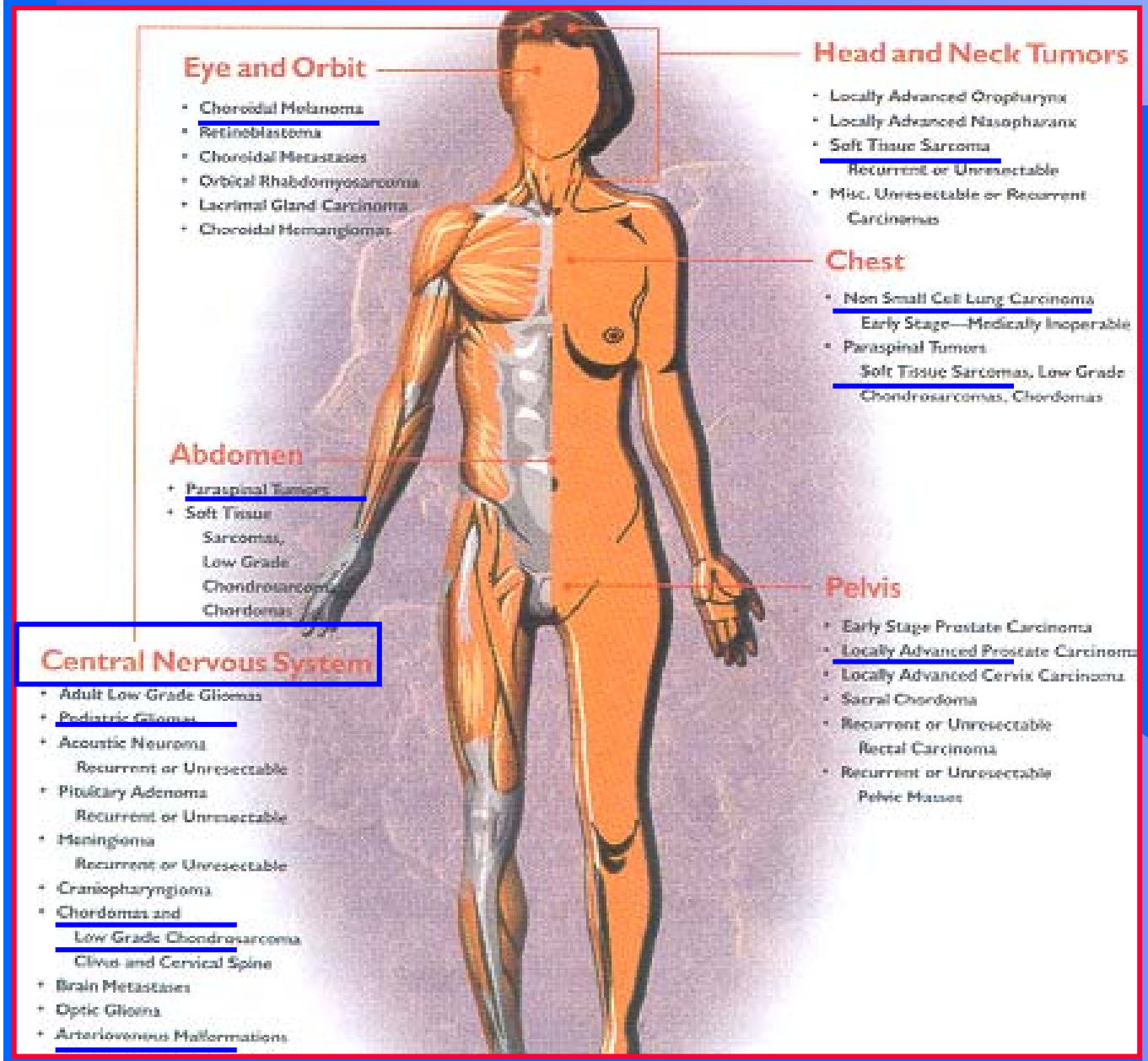
HIT at Heidelberg

First beam extracted in 2007

First patient: end 2008



The sites treated with hadrons



In the world

protontherapy:

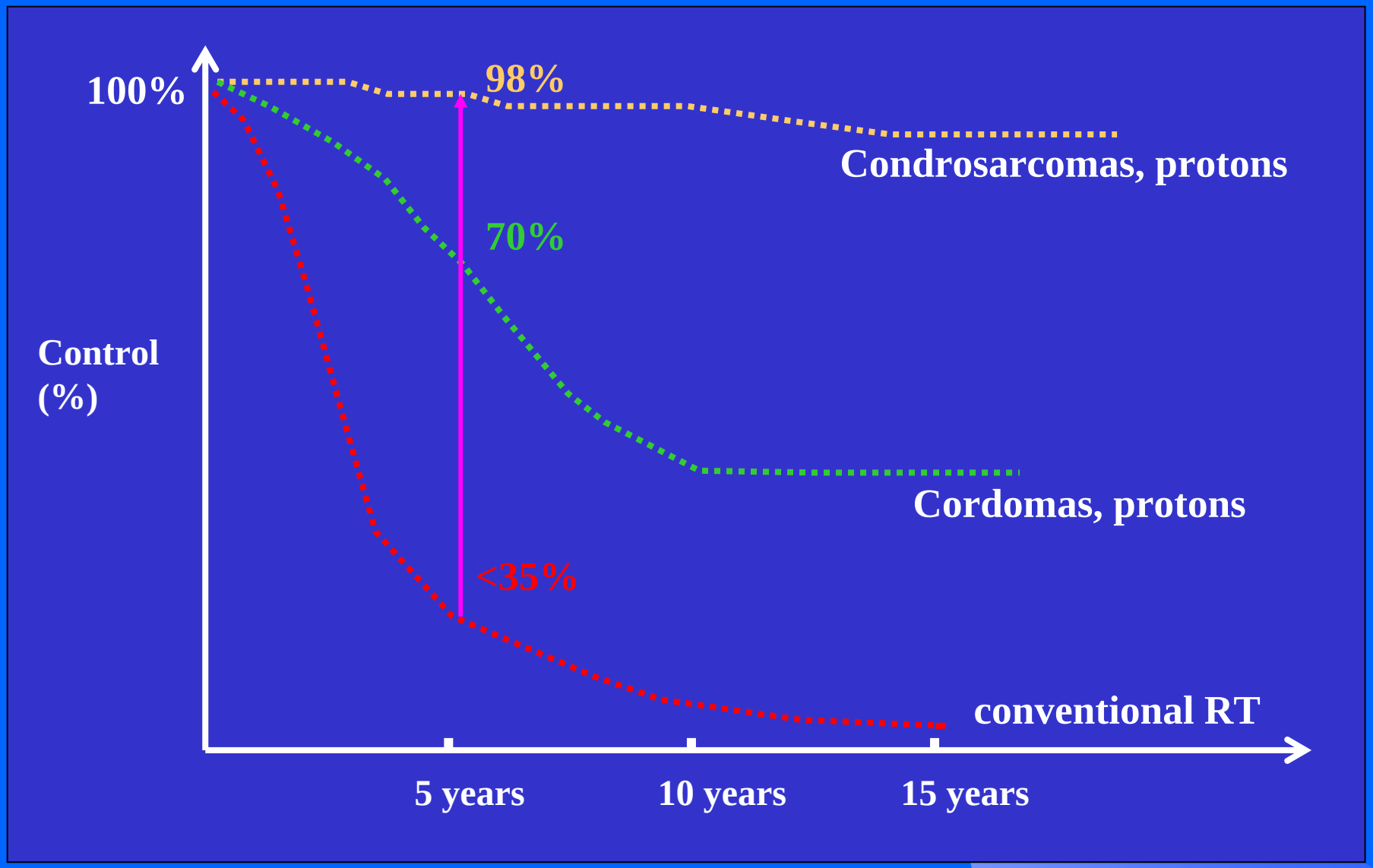
55'000 patients

carbon ion

therapy

4500 patients

First important results obtained with protontherapy



Elective indications for carbon ion therapy from HIMAC and GSI

Hirohito H. Tsujii (May 2007):

for all these tumours we can obtain a 90% local control with no severe complications

Jürgen Debus

- **Chordoma / low grade chondrosarcoma**
- **Malignant salivary gland tumors**
- **Malignant melanoma of the paranasal sinus**
- **Soft tissue sarcomas and bone tumors**
- **Lung cancer (150 patients treated in 1 fraction: NO REPAIR!)**
- **Liver tumors**
- **Prostate carcinoma**

Indication	End point	Results photons	Results carbon HIMAC-NIRS	Results carbon GSI
Chordoma	local control rate	30 – 50 %	65 %	70 %
Chondrosarcoma	local control rate	33 %	88 %	89 %
Nasopharynx carcinoma	5 year survival	40 -50 %	63 %	
Glioblastoma	av. survival time	12 months	16 months	
Choroid melanoma	local control rate	95 %	96 % (*)	
Paranasal sinuses tumours	local control rate	21 %	63 %	
Pancreatic carcinoma	av. survival time	6.5 months	7.8 months	
Liver tumours	5 year survival	23 %	100 %	
Salivary gland tumours	local control rate	24-28 %	61 %	77 %
Soft-tissue carcinoma	5 year survival	31 – 75 %	52 -83 %	

Table by G. Kraft - 2007

(*) Preservation of eyesight

Numbers of potential patients

X-ray therapy

every 10 million inhabitants: 20'000 pts/year

Protontherapy

12% of X-ray patients 2'400 pts/year

Therapy with Carbon ions for radio-resistant tumour

3% of X-ray patients 600 pts/year

TOTAL every 10 M **about 3'000 pts/year (*)**

(*) In Italy : 17'000 patients
5 proton centres and 1 carbon centre (AIRO-2004)

TERA programmes since 1992

TERA has proposed and designed the 'dual' National Centre for carbon ions and protons

1. CNAO is being built in Pavia

TERA has introduced and developed a novel type of accelerator:

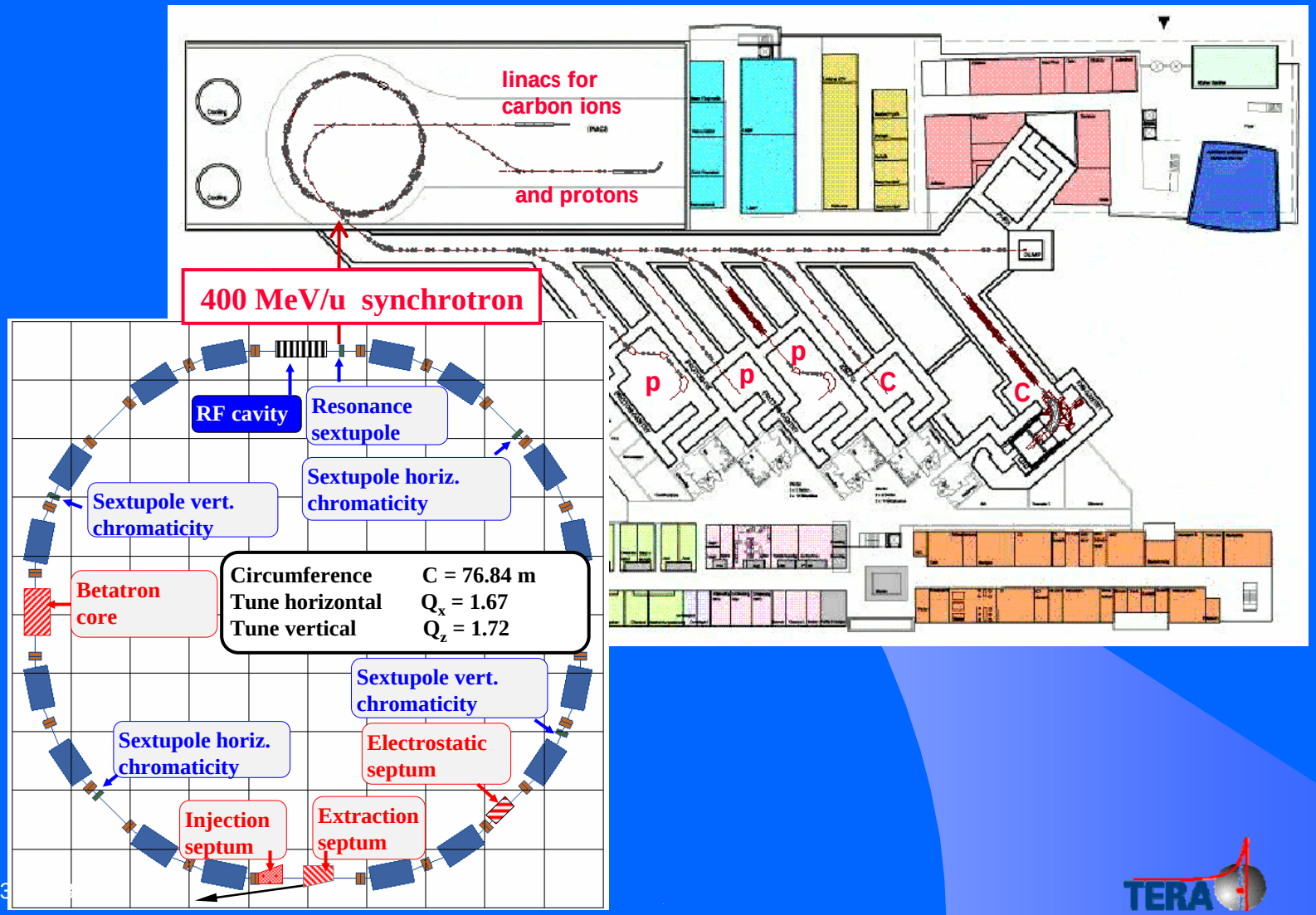
the "cyclinac"

2. "cyclinacs for protons and carbon ions

PIMMS at CERN in 1996 - 2000

CERN–TERA–MedAustron Collaboration for optimized medical synchrotron

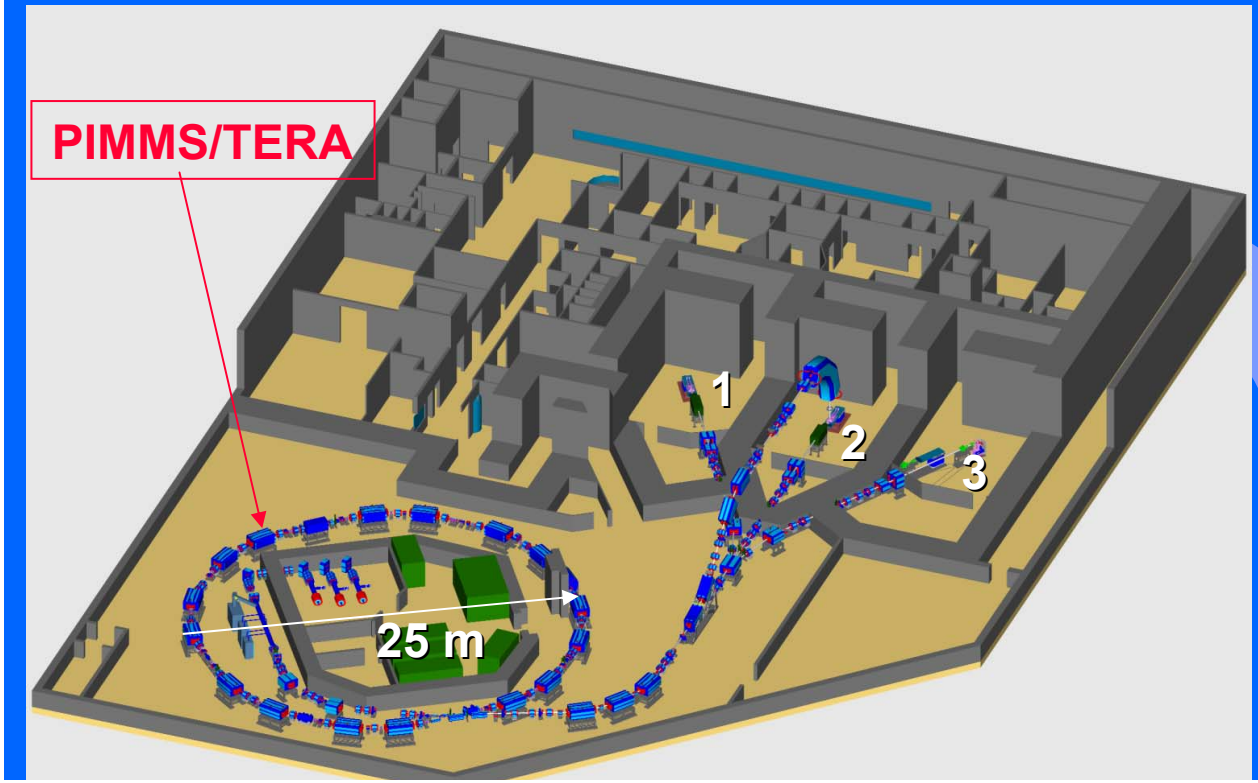
Project leader: P. Bryant



CNAO = Centro Nazionale di Adroterapia

CNAO Foundation created by the Italian Government in 2002:
4 Hospitals in Milan, 1 Hospital in Pavia and TERA

In October 2003 TERA passed to CNAO
the design of CNAO (3000 pages) and 25 people



Since 2004 INFN is "Istitutional Participant" with people and important construction responsabilities

(Caudio Sanelli)

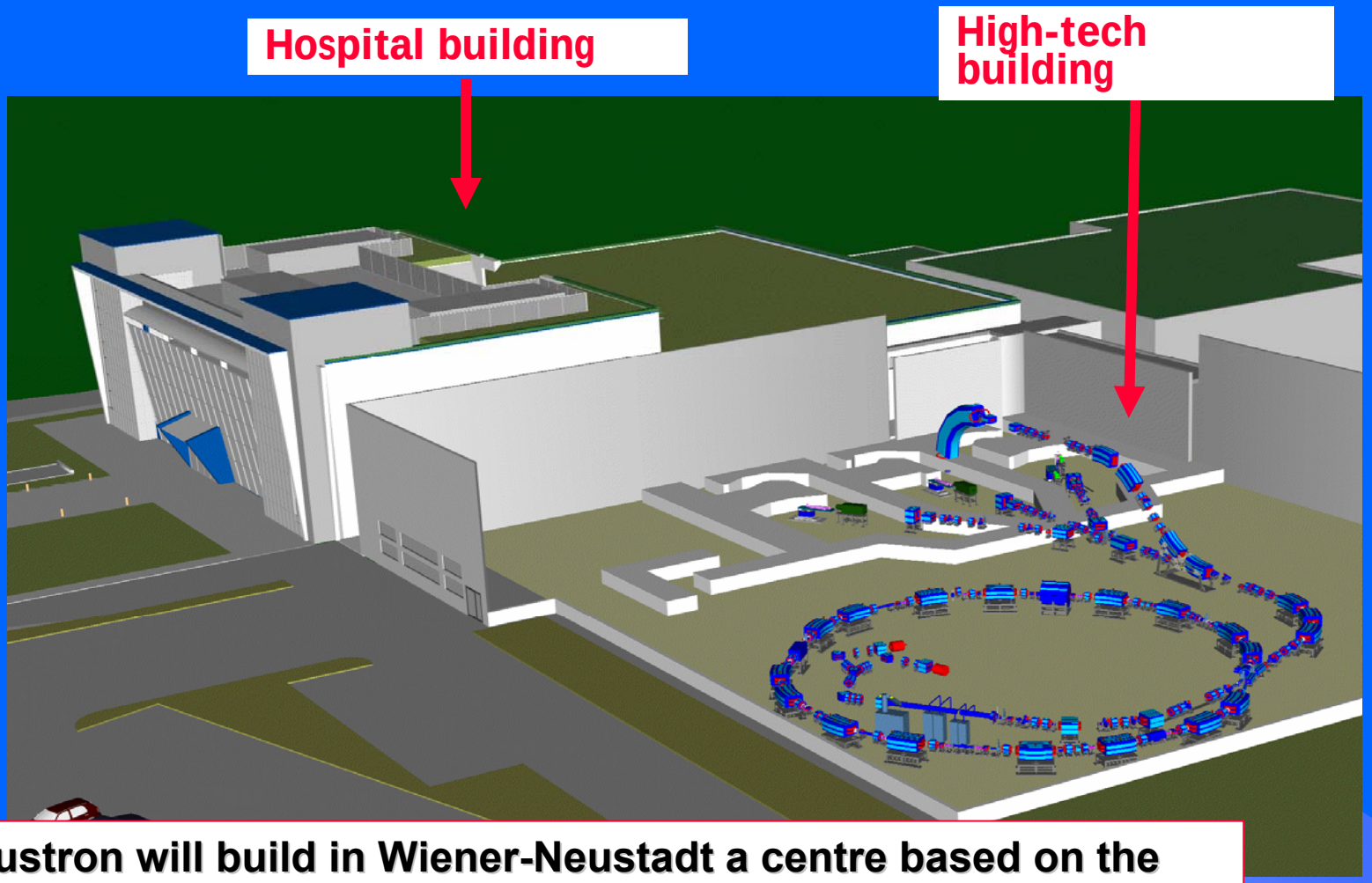
INFN runs CATANA for eye protontherapy in Catania

TERA

The CNAO Foundation constructs the Centre

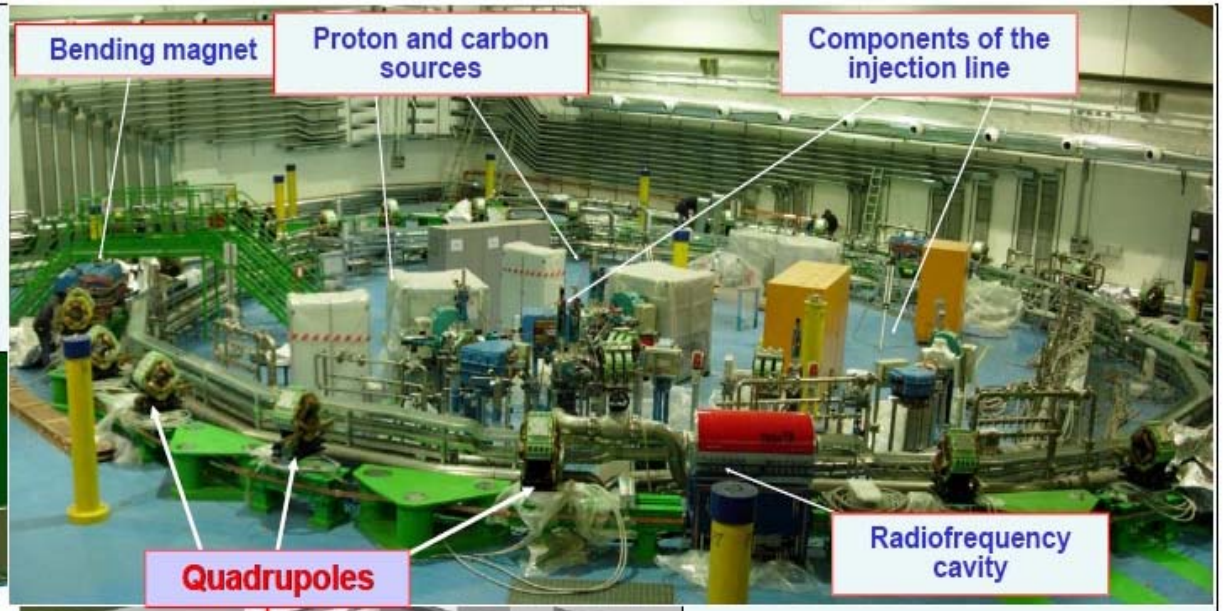
President: Erminio Borloni

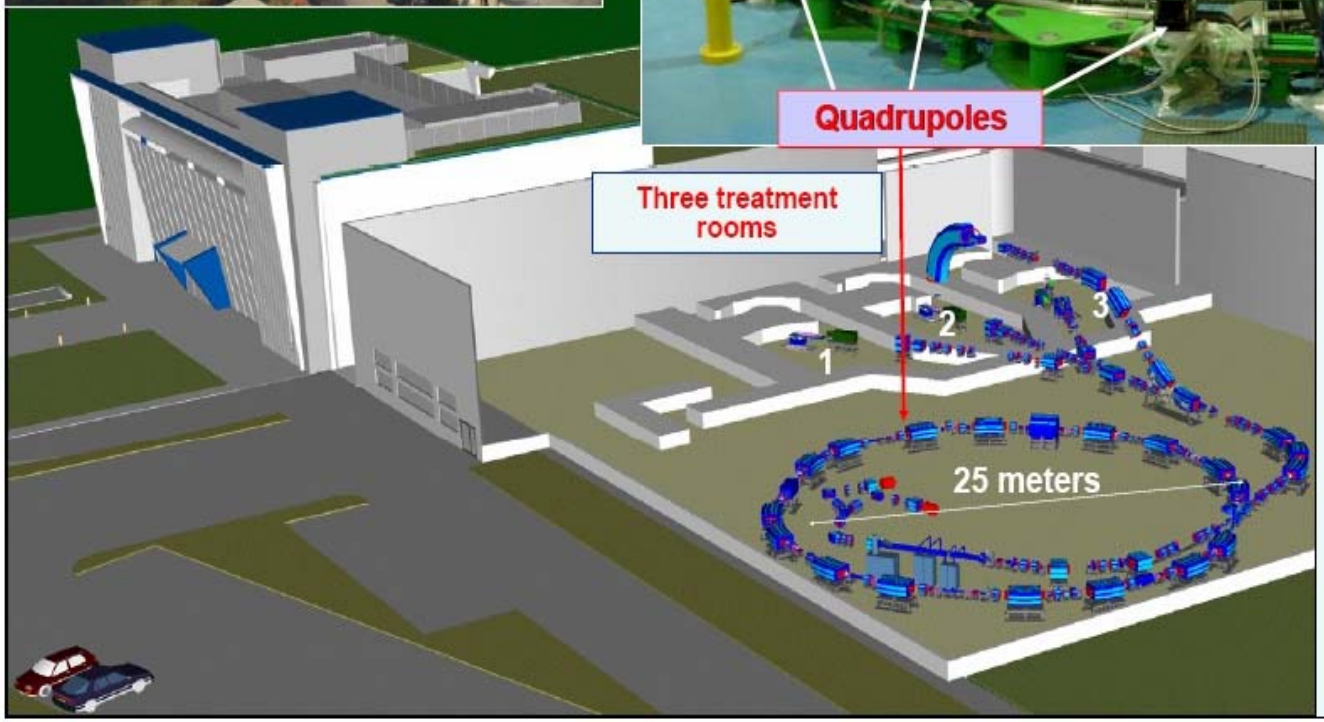
Medical Director: Roberto Orecchia Technical Director: Sandro Rossi



MedAustron will build in Wiener-Neustadt a centre based on the CNAO construction drawings (CERN-CNAO-INFN Agreement)

CNAO status in February 2008





CNAO
Centro Nazionale di Adroterapia Oncologica
Pavia

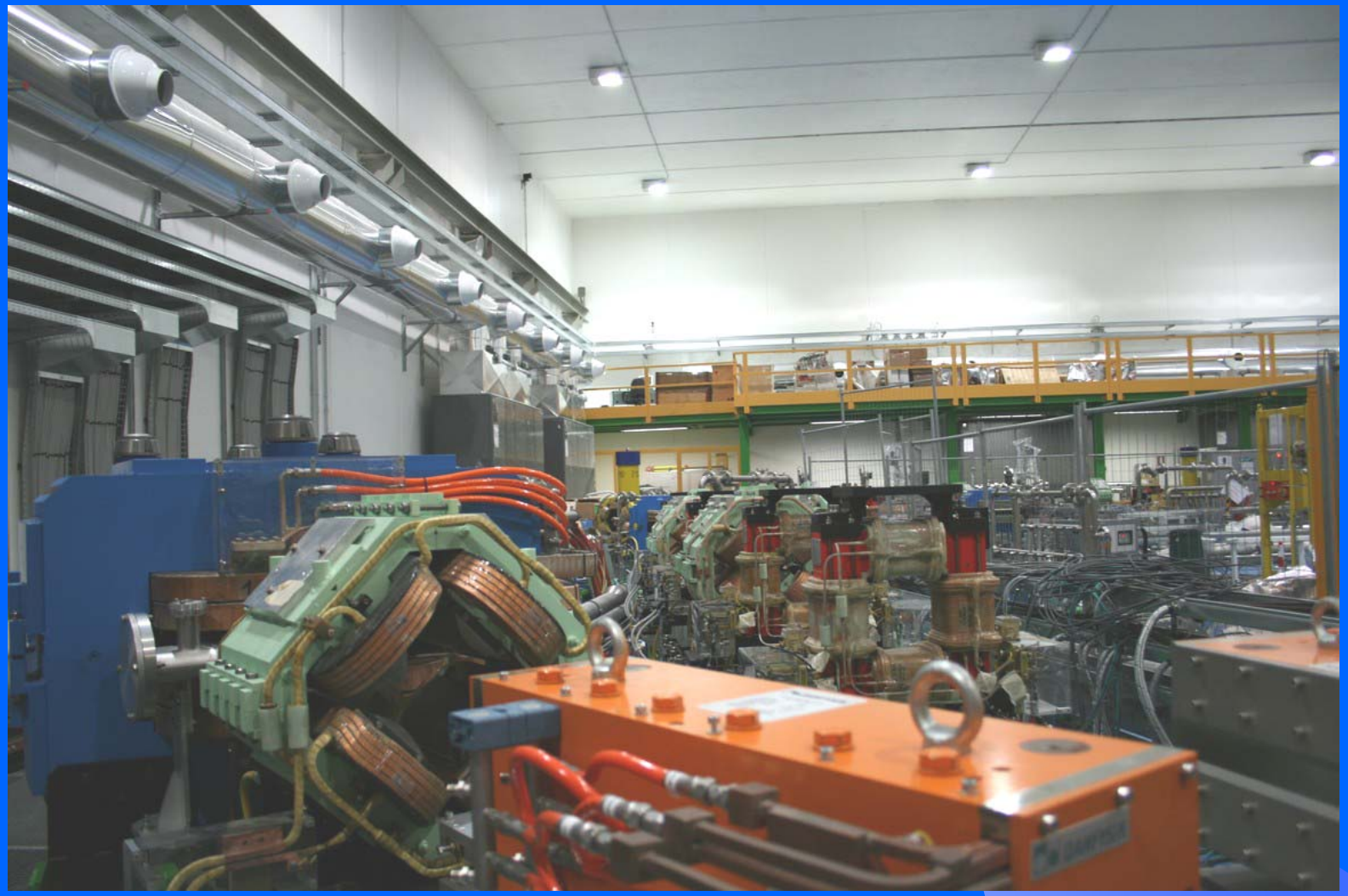
100 M€

80% from Health Ministry

CNAO status in October 2008

Hospital Building

The synchrotron area



The vertical beam

First patient: end of 2009

ENLIGHT and the European projects

European Network for LIGht-ion Hadron Therapy – 2002 - 2005

- GSI project for the University of Heidelberg Clinics (in commissioning)
- TERA project for CNAO in Pavia (in construction)
- Marburg University (in construction by Siemens Medical)
- Med-Austron for Wiener Neustadt (approved)
  partner of PIMMS since 1996 – Agreement with CNAO
- ETOILE in Lyon (approved)
  Competitive tendering

SINCE 2006 THESE GROUPS + CERN + GSI AND MANY OTHERS ARE PART OF THE

ENLIGHT ++ PLATFORM CO-ORDINATD BY Dr. MANJIT DOSANJH

APPROVED FP7 : PARTNER AND ULICE

THE END