Hadron Therapy

for Cancer Treatment

G. P. Yeh

Fermi Lab

Robert R. Wilson

Founding Director, Fermi Lab

National Medal of Science

Pulse

ACCELERATOR SCIENCE IN MEDICINE

www.fnal.gov/pub/pulse

1954 First Hadron Therapy

Ernest Lawrence

John H. Lawrence

Cornelius Anthony Tobias

Radiological Use of Fast Protons

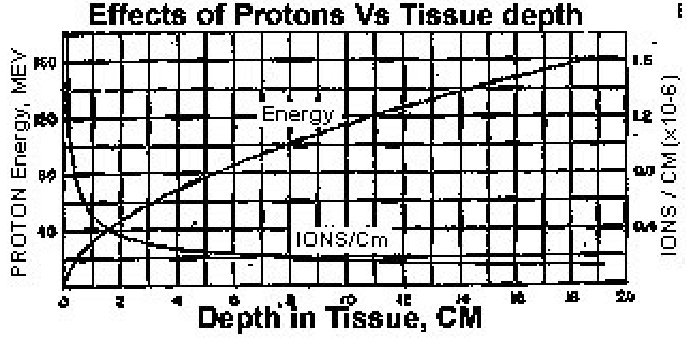
ROBERT R WILSON
Research Laboratory of Physics, Harvard University Cambridge, Massachusetts
Accepted for publication in July 1946.

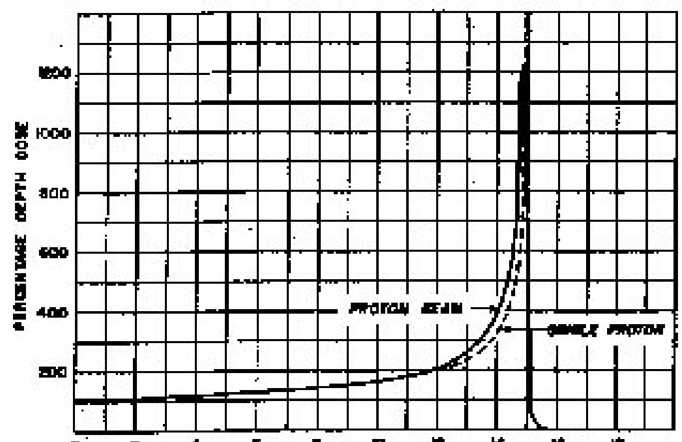
Except for electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in large part, been due to the very short penetration in tissue of protons, deuterons, and alpha particles from present accelerators.

Higher-energy machines are now under construction, however, and the ions from them will in general be energetic enough to have a range in tissue comparable to body dimensions. It must have occurred to many people that the particles themselves now become of considerable therapeutic interest. The object of this paper is to acquaint medical and biological workers with some of the physical properties and possibilities of such rays.

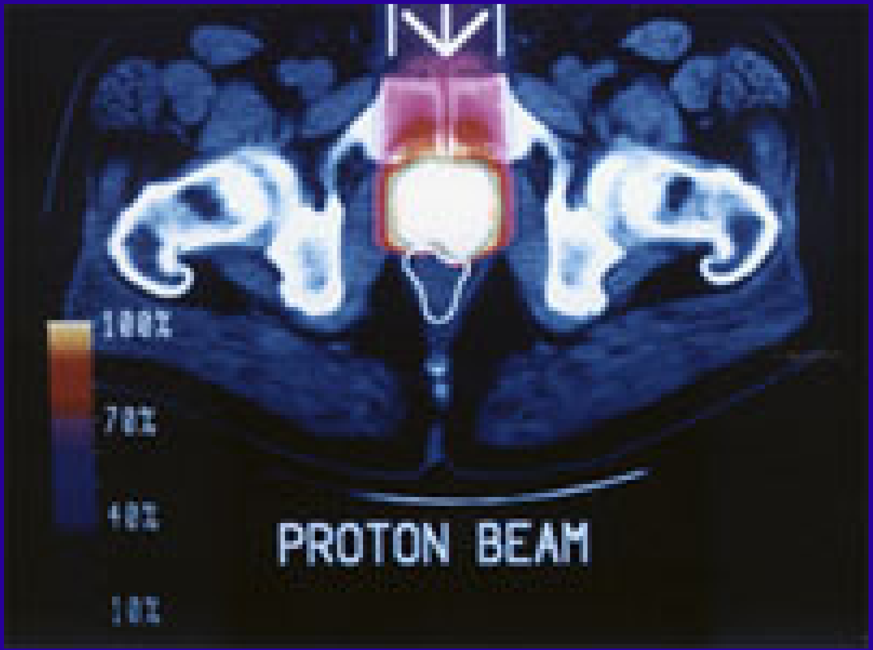
To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 MeV (million electron volts) and perhaps as high as 400 MeV. The range of a 125 MeV proton in tissue is 12 cm., while that of a 200 MeV proton is 27 cm. It is clear that such protons can penetrate to any part of the body.

Effects of Protons Vs Tissue depth





Dosage due to 140 MEV Protons in tissue



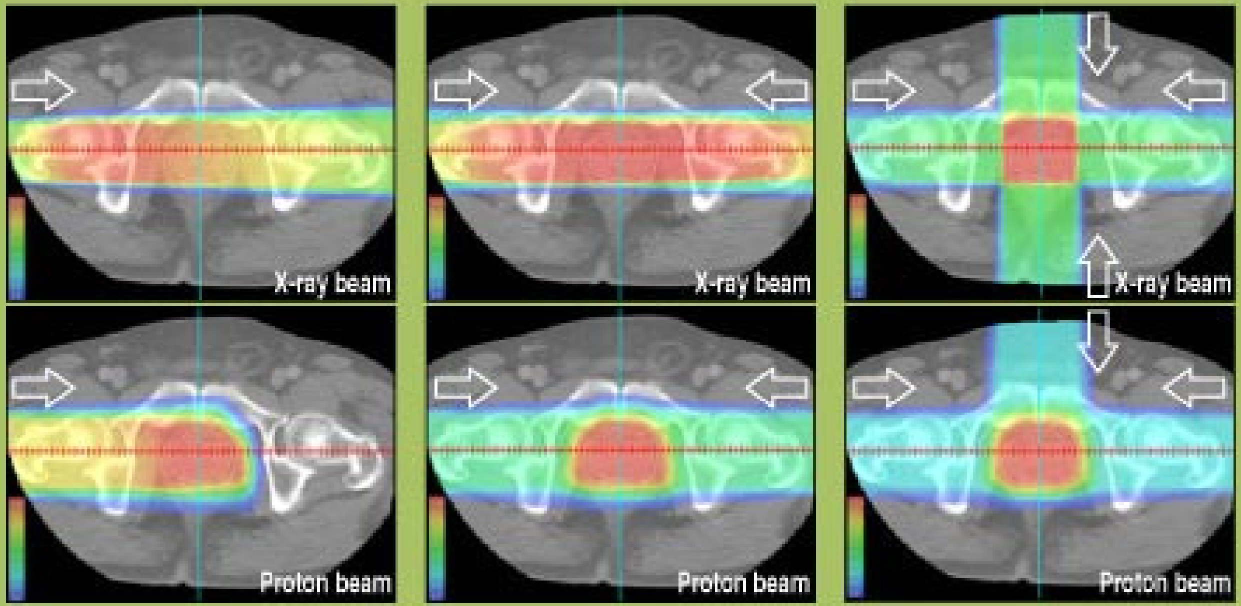
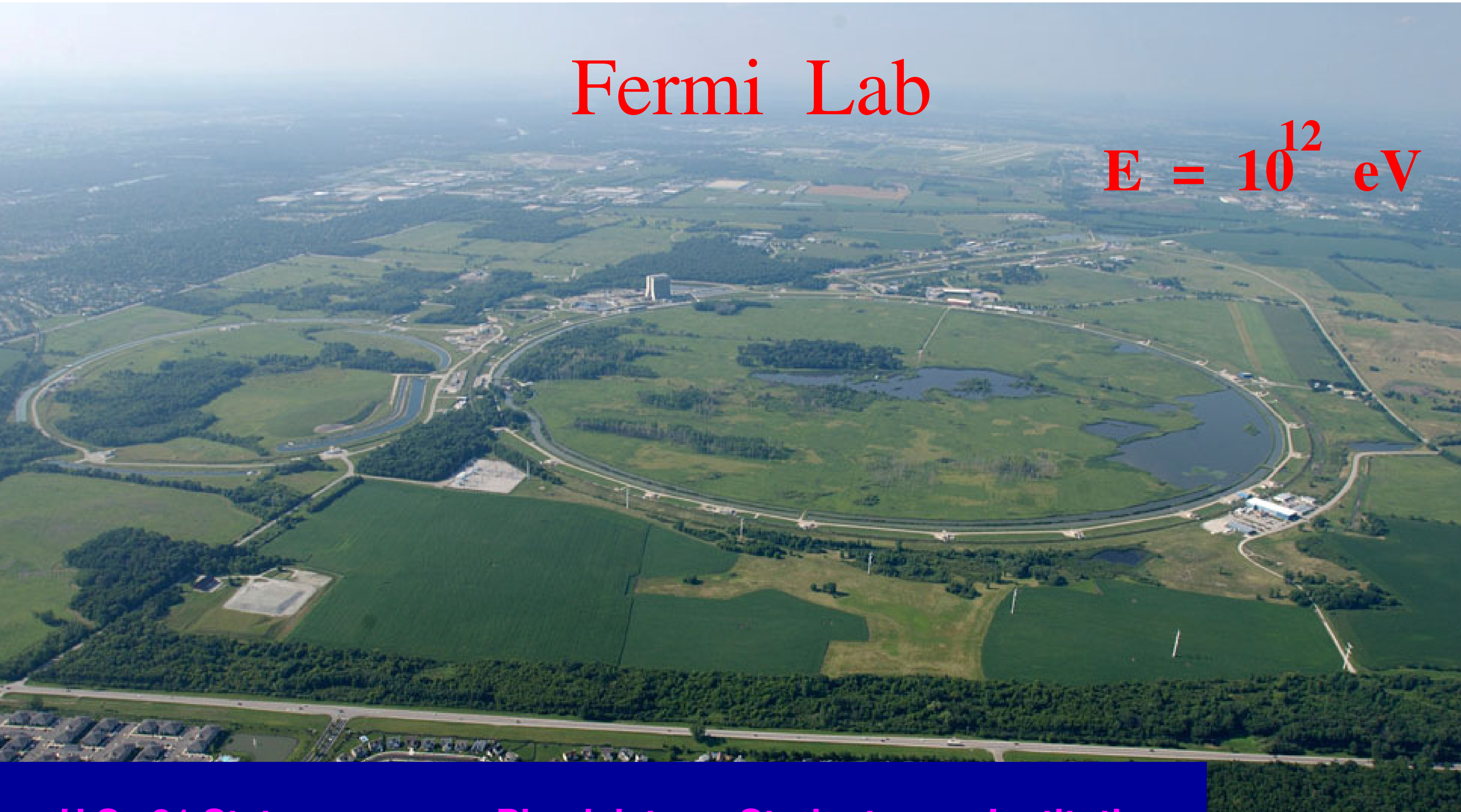


Fig. X-ray beam vs. Proton beam for prostate cancer

Fermi Lab

$E = 10^{12}$ eV



U.S. 31 States	Physicists	Students	Institutions
Universities	721	398	94
National Labs	386	16	7

40 other Countries	Physicists	Students	Institutions
Universities	468	178	90
National Labs	301	36	23

Quarks :	u	c	$\mathbf{t}$
	d	s	b
Leptons:	ν_e	ν_μ	ν_τ
	e	μ	τ

Gauge bosons : γ g $W^\pm$ Z^0 G

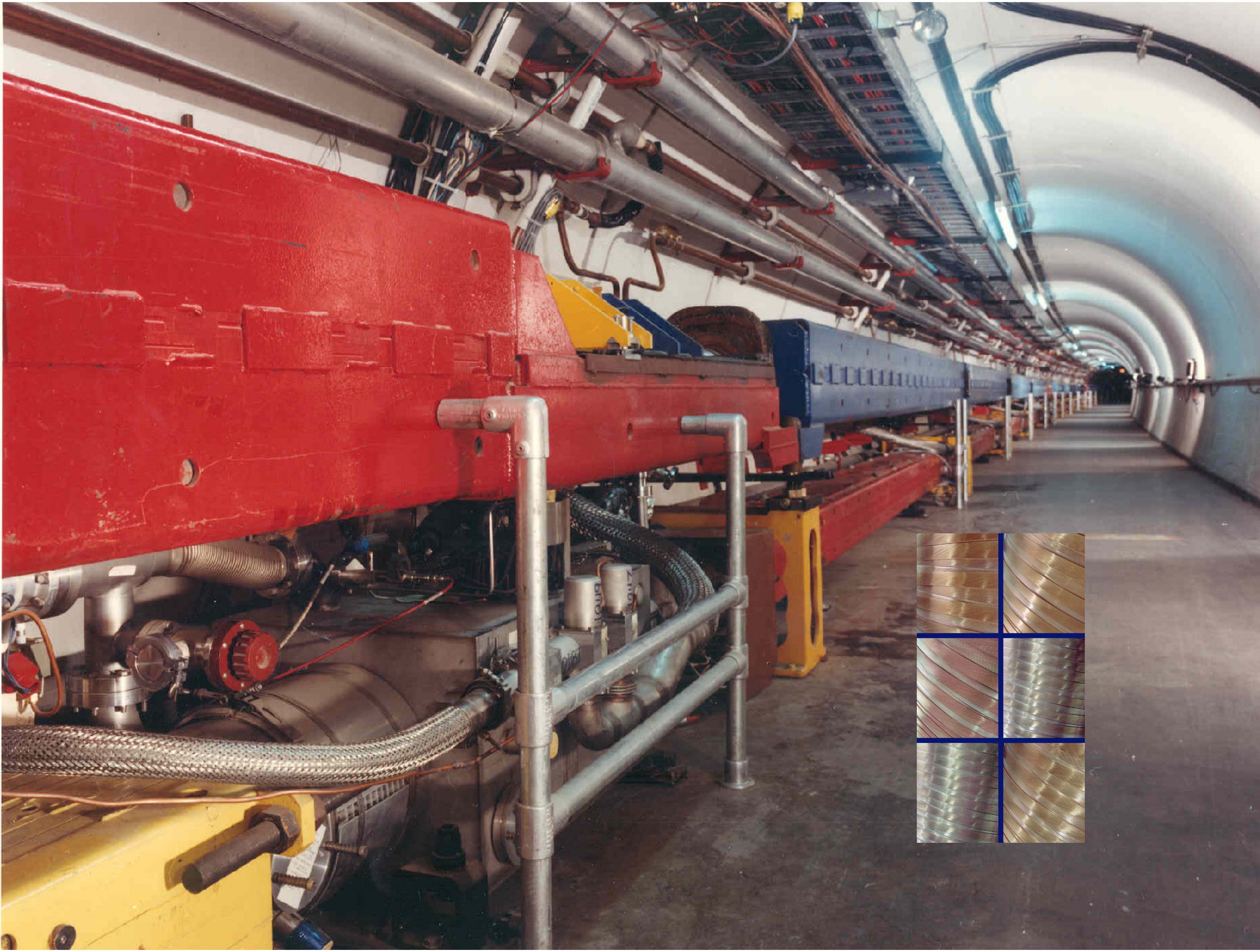
Higgs

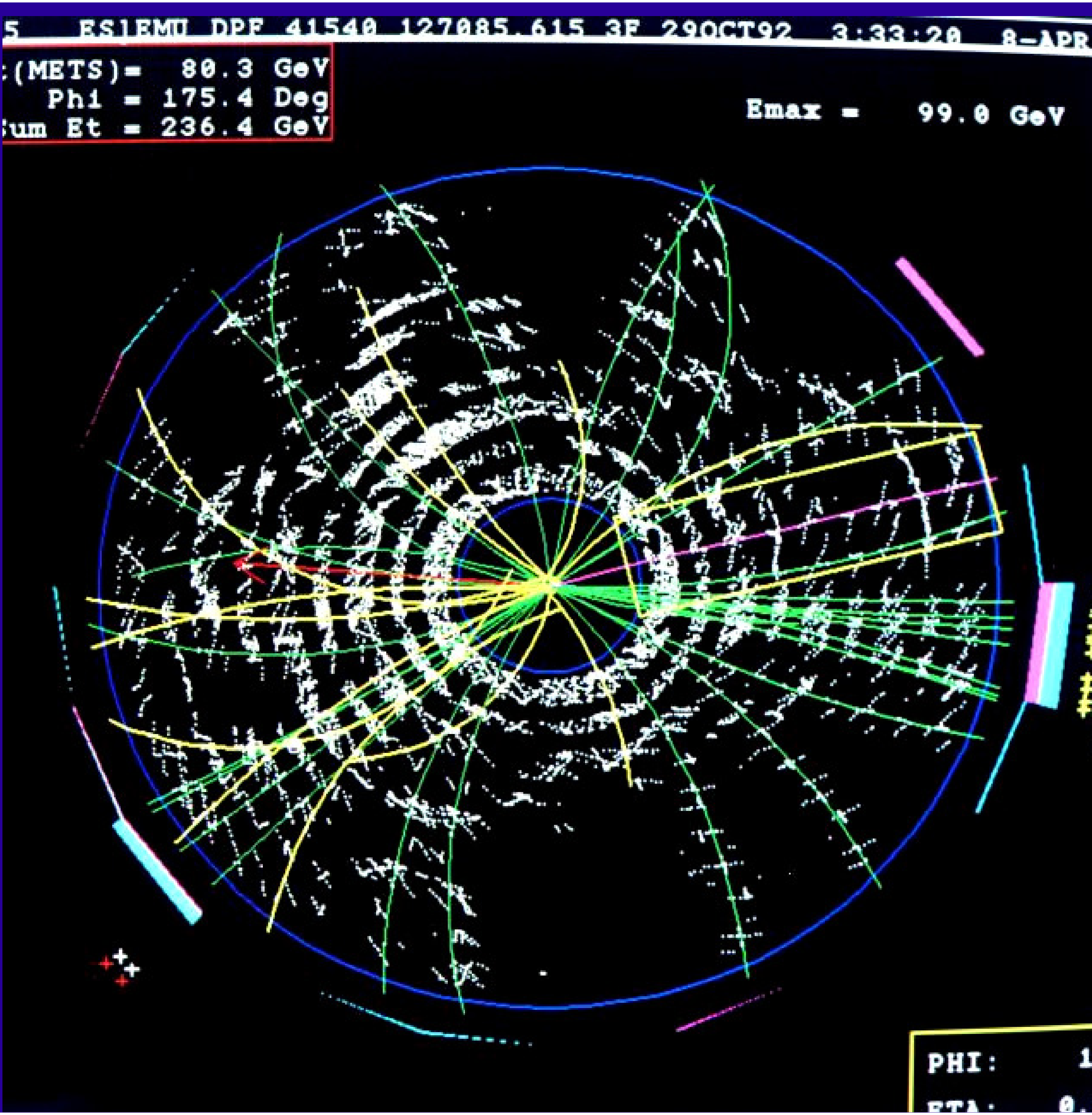
1897	e
1937	μ
56	ν_e
62	ν_μ
68	quarks and g inside p, n
74	c
75	τ
77	b
79	g
1983	$W^\pm$ Z^0
1995	$\mathbf{t}$
?	Higgs
?	SUSY

Space - Time

Quarks & Leptons	$<$	10^{-17}	cm
Atom		10^{-8}	
Apple	$5\times$	10^{0}	
Earth	$6\times$	10^{8}	
Universe		10^{28}	

Top Quark		10^{-24}	sec
b quark		10^{-12}	
proton	$>$	10^{+40}	
person	$3\times$	10^{9}	
Universe	$5\times$	10^{17}	





The first Top Quark

1 top quark

In 10^{12} collisions

Discovery of the Top Quark

``World domination begins at Fermi Lab''

A Geek In Paradise

Figure 1. Fermi Campus

A trip to see the particle accelerator at Fermilabs by a self-professed geek.

by Jon "maddog" Hall

I had been to Fermilab only the year before, but when the invitation came from Dan Yocum to meet at Fermilab's facility outside Chicago, how could I refuse? I am a geek at heart.

Figure 2. Dr. G.P. Yeh (third from the left) and Linux supporters: Ruediger Oertel from SuSE, Fermilab System Administrator, G.P. Yeh, Stefan Traby from Quant-X, Larry Augustin from VA Linux Systems, Norman Jacobowitz, Linus Torvalds, Dan Yocum, maddog and Matthew Cunningham

Fermilab is short for "Fermi National Accelerator Laboratory", located in Batavia, Illinois. It occupies a parcel of land about three miles on each side (see Figure 1), and houses several accelerator rings which generate (in a *very* concentrated space) amounts of power greater than those found in the sun or any other place in the galaxy, much less on the face of the earth. They use these fantastic amounts of power to collide various particles at extremely high speed in the search for the basic building blocks of the universe.

Figure 3. No, it's not a set from *Star Wars, Episode 1*, it's the Fermi main building.

In ancient days, various philosophers stated that we would eventually find the "smallest particle", and for a while this was considered to be the atom. In the relatively recent days of discovering nuclear energy, it was recognized that the smallest particle was *not* the atom, but made up of various other parts such as protons, neutrons and electrons. (Students of physics, please have mercy on me as I try to explain this in words that most readers will understand.) During the last quarter of a century, more and more physicists began to believe there were even smaller particles making up the protons, called quarks and gluons. Quarks (having nothing to do with a resident of *Deep Space Nine*) are thought to have six different types, and in 1994 the last of these Quarks, the "top quark", was discovered at Fermilab. Unfortunately, the top quark exists for only a very short (10^{-24} seconds) period of time, so it is very hard to collect data on it, particularly when it is seen only six times in a given year of running the accelerator. Therefore, Fermilab decided to increase the size and power of its accelerator, so it could see anywhere from 20 to 300 times the number of quarks. Unfortunately, this would take anywhere from 20 to 300 times the amount of power and generate 20 to 300 times the amount of raw data to be seen by the collectors, meaning 1,000,000MB of data would be generated every second. Yes, that is one million megabytes of data per second.

Of course, storing that much data would be very difficult, but fortunately Fermilab had determined they would be able to filter the information and store a smaller subset of it (only 18 to 100MB of data per second) for later analysis. To do this, they would have to increase the power of their computing systems significantly, and their former model of using expensive workstations in a workstation farm would not have been affordable. Enter Linux.

Last year, when people from Red Hat Software and I visited Fermilab while attending Spring Comdex, I was lucky enough to meet G. P. Yeh, a big fan of Linux and one of the physicists who discovered the top quark. He was kind enough to take us on a short tour of the Fermilab facilities and explain the role of Linux within Fermilab. He explained they investigated Linux and proved that inexpensive PCs running Linux could do the job more than adequately for a price they could afford. They estimated they would need about 2,000 CPUs working together.

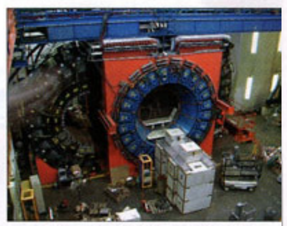


Figure 4. Collider Rings

This year, when Dan Yocum heard that Linus Torvalds was speaking at Spring Comdex, he enlisted my help in convincing Linus to make a separate trip to Fermilab to speak to the physicists and their families. This did not take much convincing, since Linus has an interest in math, physics and science.

We met at the hotel where Linus was staying, and with a small group of Linux supporters (see Figure 2), drove to Fermilab. It is quite interesting to approach Fermilab, since the land around the accelerator is flat, with only the main building (see Figure 3) rising up from the ground to any height. It would definitely be a great scene for a science fiction movie.

We parked the car, went inside and met Dr. G. P. Yeh (who everyone calls "G.P.").

G.P. took us on an extended tour, beginning with the top floor of the main building, looking out over the collider rings. "As far as you can see in every direction is Fermilab", G.P. said. It was an impressive sight. He then took us to see the collider detectors (see Figure 4)—"It weighs only 100 tons and cost about 100 million dollars." Finally, we visited the computer room, where the Linux Farms were going to be placed (see Figures 5 and 6). Fermilab calls their systems "Farms" rather than Beowulf systems. They have master machines that delegate the work to many slave processors, connected by high-speed networking and switches. They are not planning on buying the 2000 CPUs until very close to the time they need them. After all, prices keep dropping and capabilities keep increasing, so why not wait until the last moment to get the best "bang for the buck"?

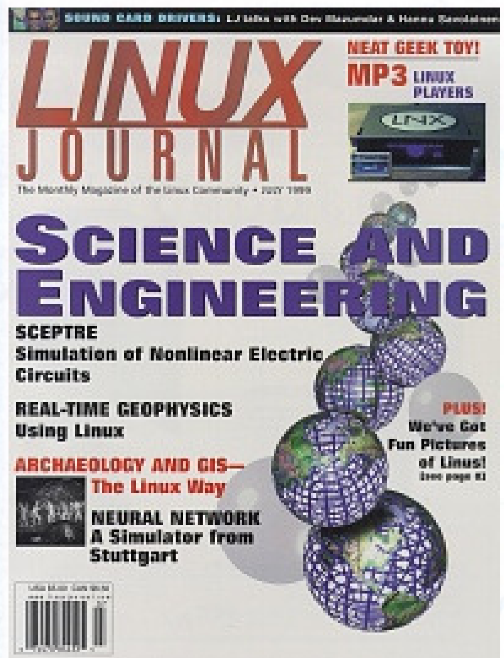
Figure 5.Computer Room–stacks of Linux boxes

Figure 6. Linux Farms: Larry Augustin from VA Linux Systems, Dan Yocum from Fermilab

After the tour was over, we went to the main auditorium where Linus gave his talk. For those of you who have heard Linus give a speech, you know he does not like to talk with prepared slides, but instead gives a short prepared talk, then answers questions. This night was no different, other than the topic and complexity of the questions. It was obvious from the questions asked that the audience had more of a computer science bent than other, more general audiences. Questions regarding symmetric multi-processing and the reality of distributing interrupts over multiple CPUs entered the air.

Figure 7. Party Time: Linus on left by lamp, G.P. Yeh in far chair, Stefan Traby in far right

Figure 8. Jeff Gerhardt's hospitality (and kitchen) were enjoyed by all.



After a significant amount of time answering questions and signing autographs, our little troupe went to the home of Jeff Gerhardt to enjoy pizza and "refreshments". We were greeted by smoke rolling out of the front door, reminding everyone it is best to take the pizza out of the box before warming it in the oven. When the smoke died down, some interesting home brew made its way to the front, and everyone enjoyed the pizza and brew (see Figures 7 and 8).

Figure 9. G.P. Yeh shows map to Linus Torvalds and Stefan Traby. World Domination begins at Fermilab!

I love this type of computing where people push the envelope of what the human mind can conceive, and I thank the government of the United States for helping to fund such a quest.

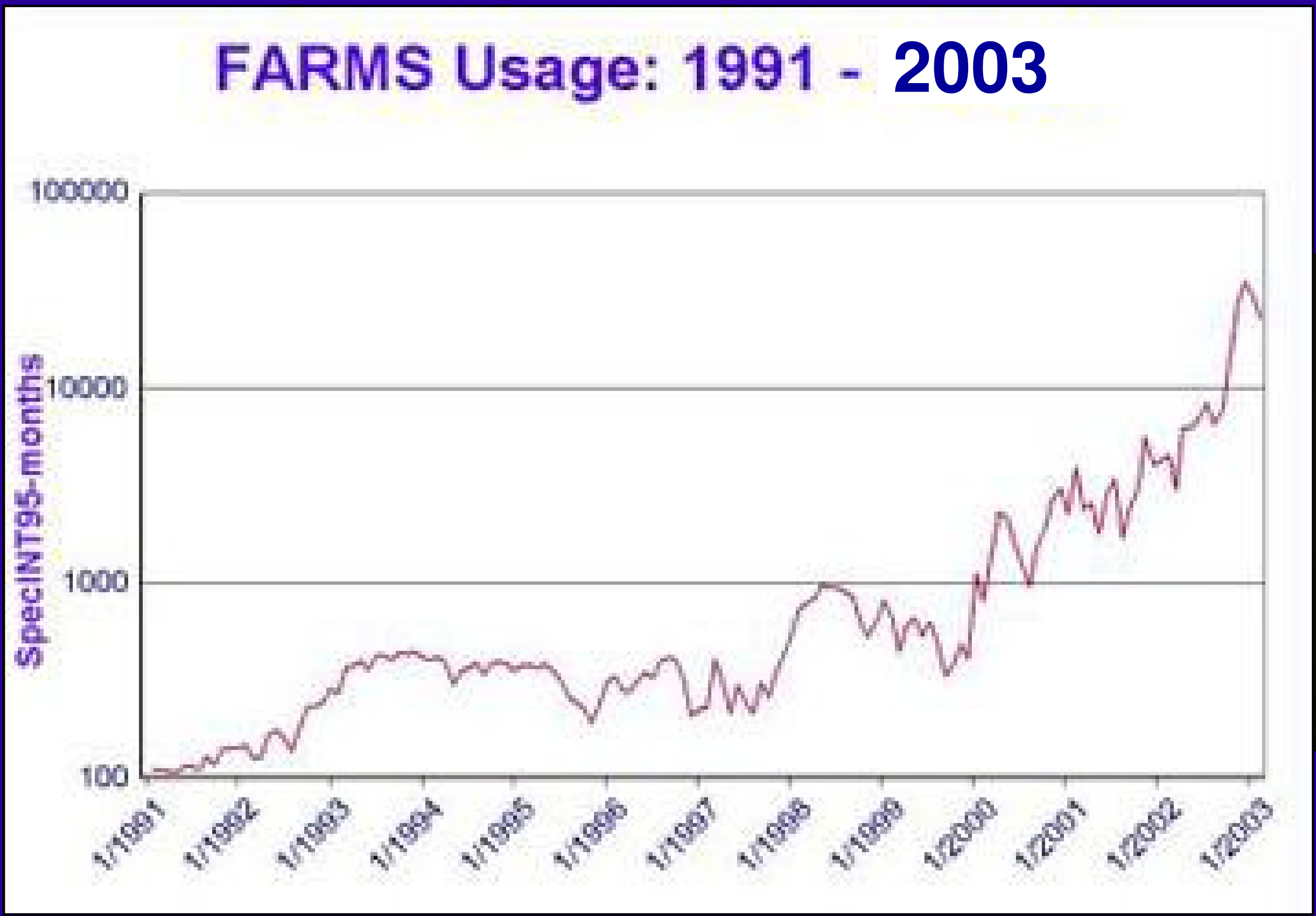
Jon "maddog" Hall is Senior Leader of Digital UNIX Base Product Marketing, Digital Equipment Corporation. He is Executive Director of Linux International.

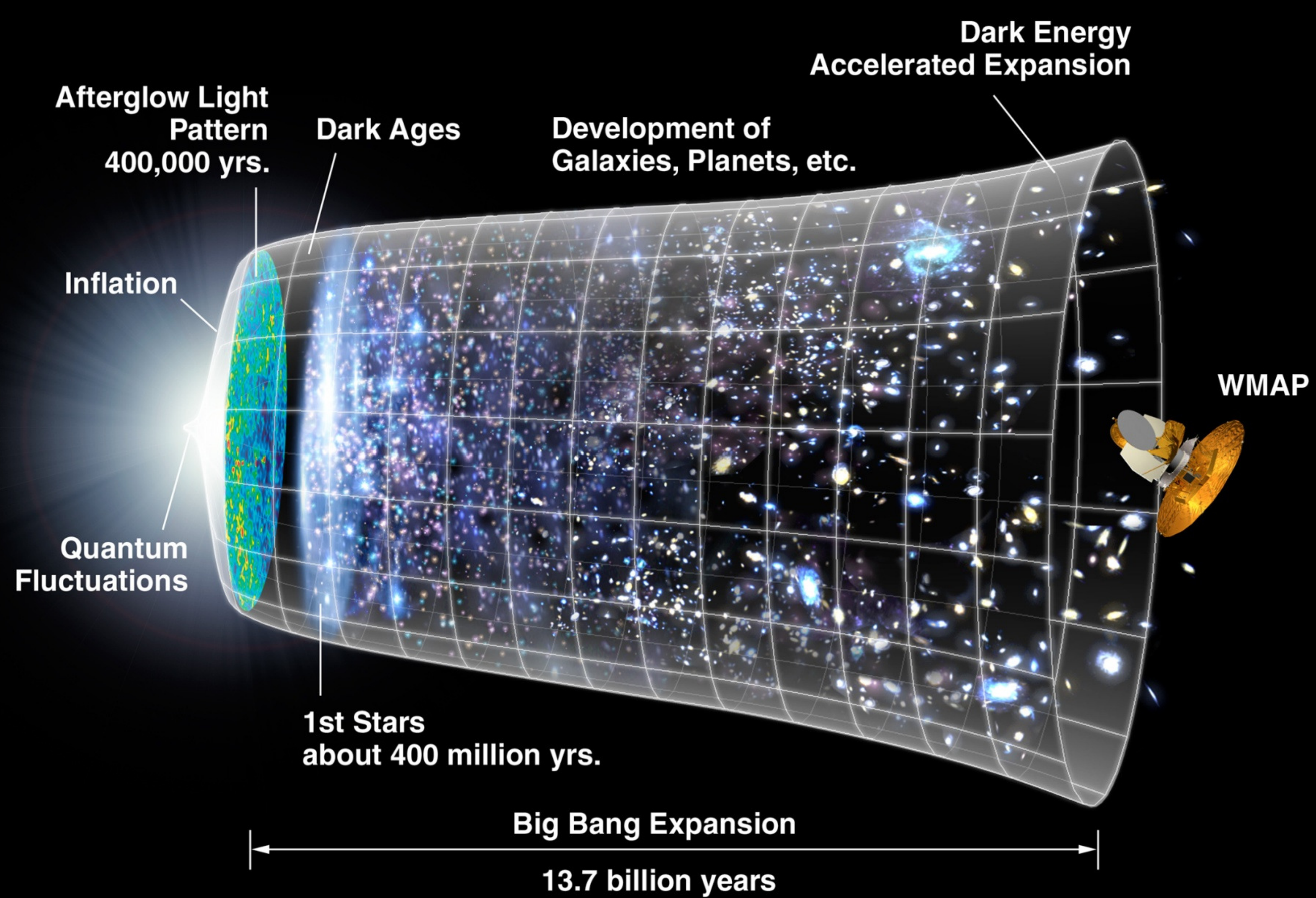
Computing Power

10^9 MegaByte
PetaByte Data Handling

Fermi Lab ⇔ world

- 300 Gbps network
- Grid Computing
- Collaboration





NASA/WMAP Science Team

World Wide Web

`` Science creates possibilities

that were not imagined previously.

In the case of the World Wide Web,

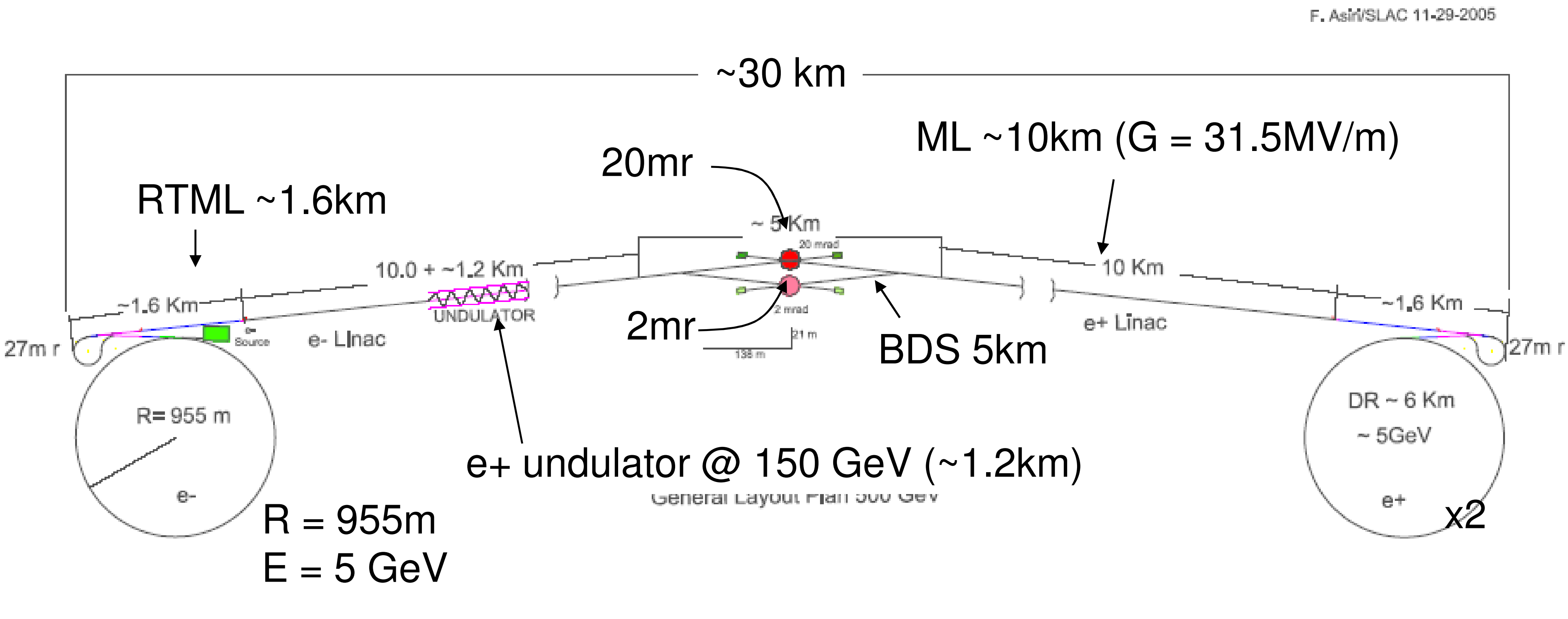
particle physicists created a great equalizing,

democratic force.''

``Science Matters" Tony Blair PM

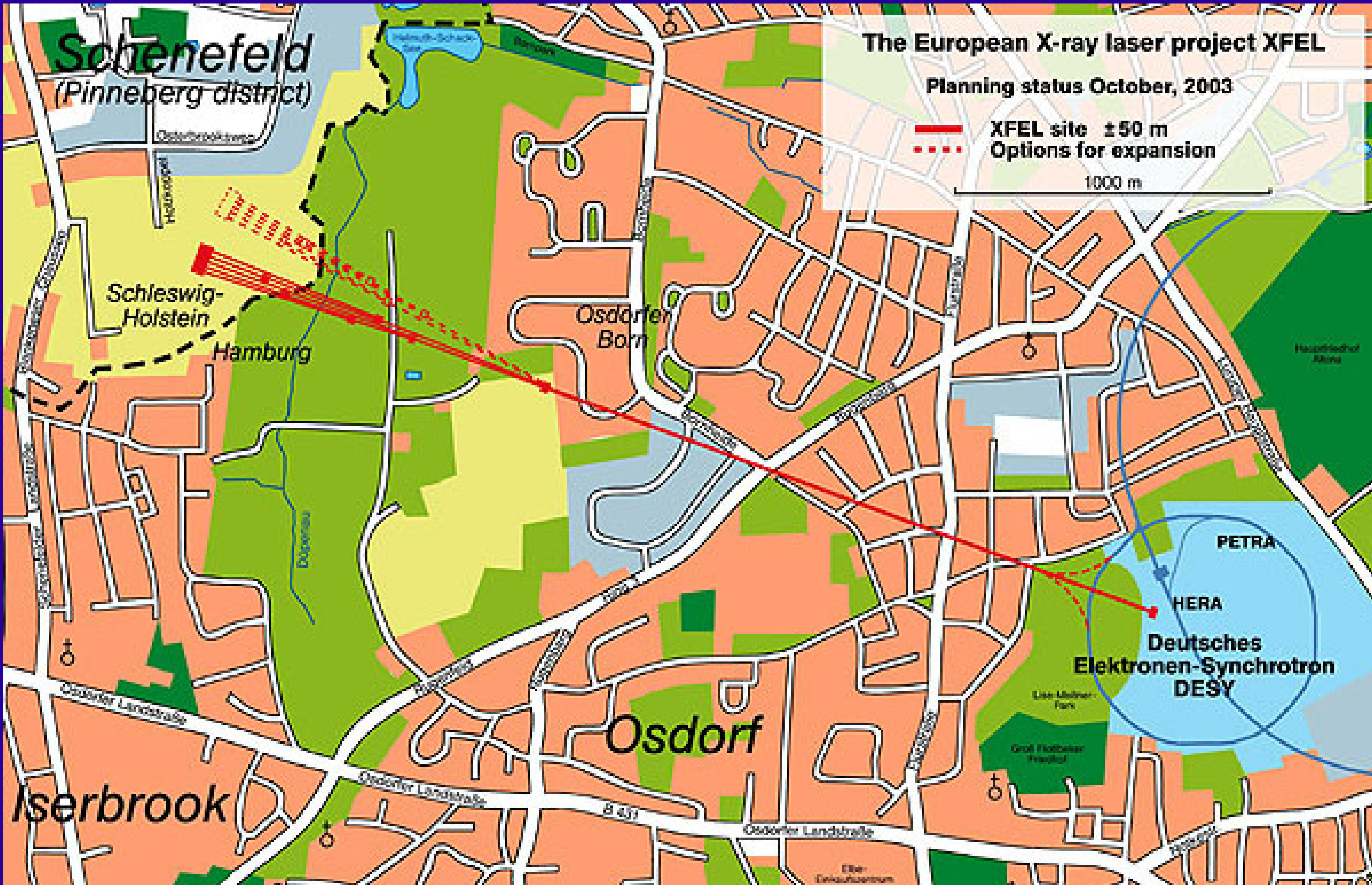
May 2002

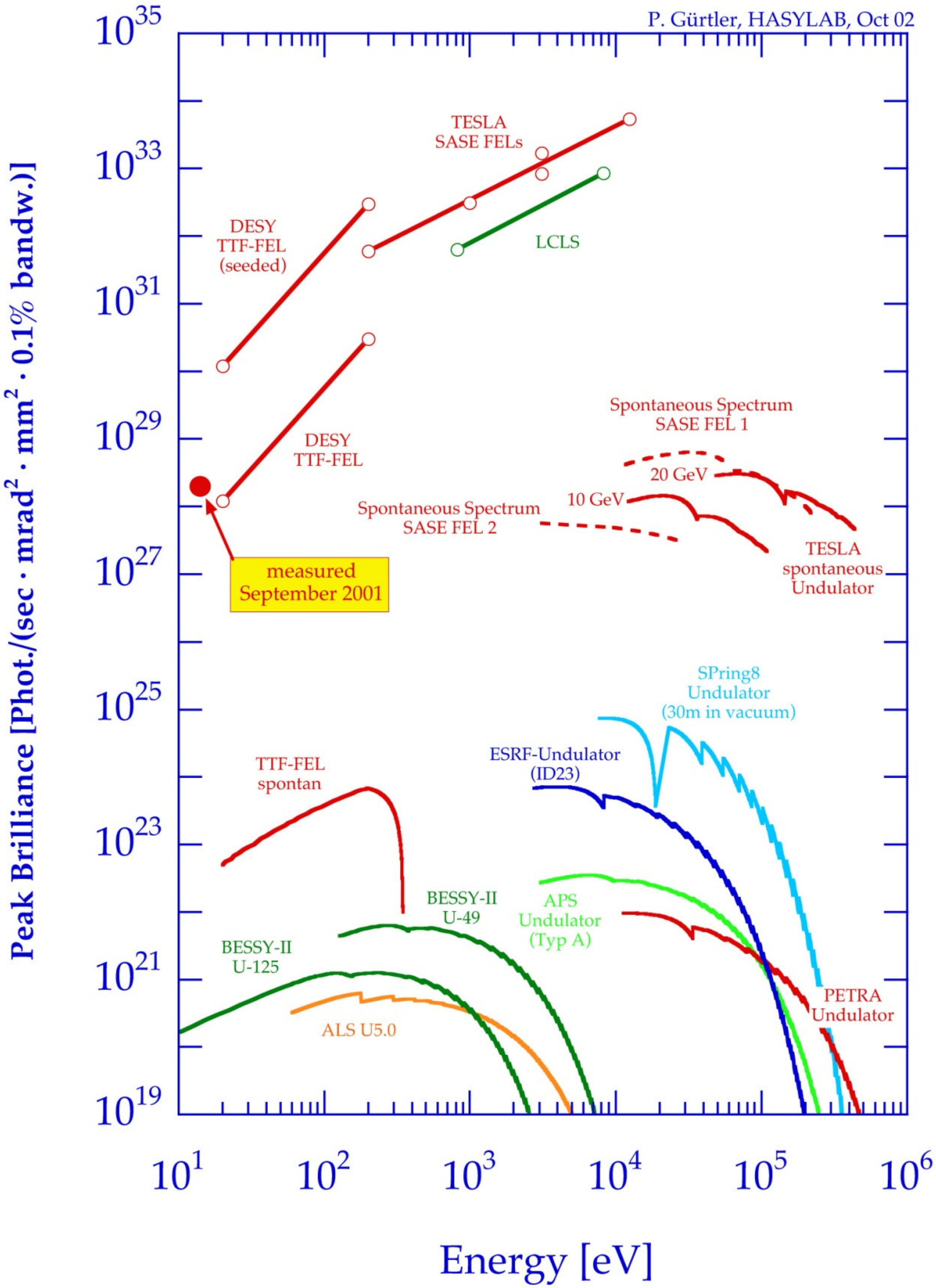
International Linear Collider ILC



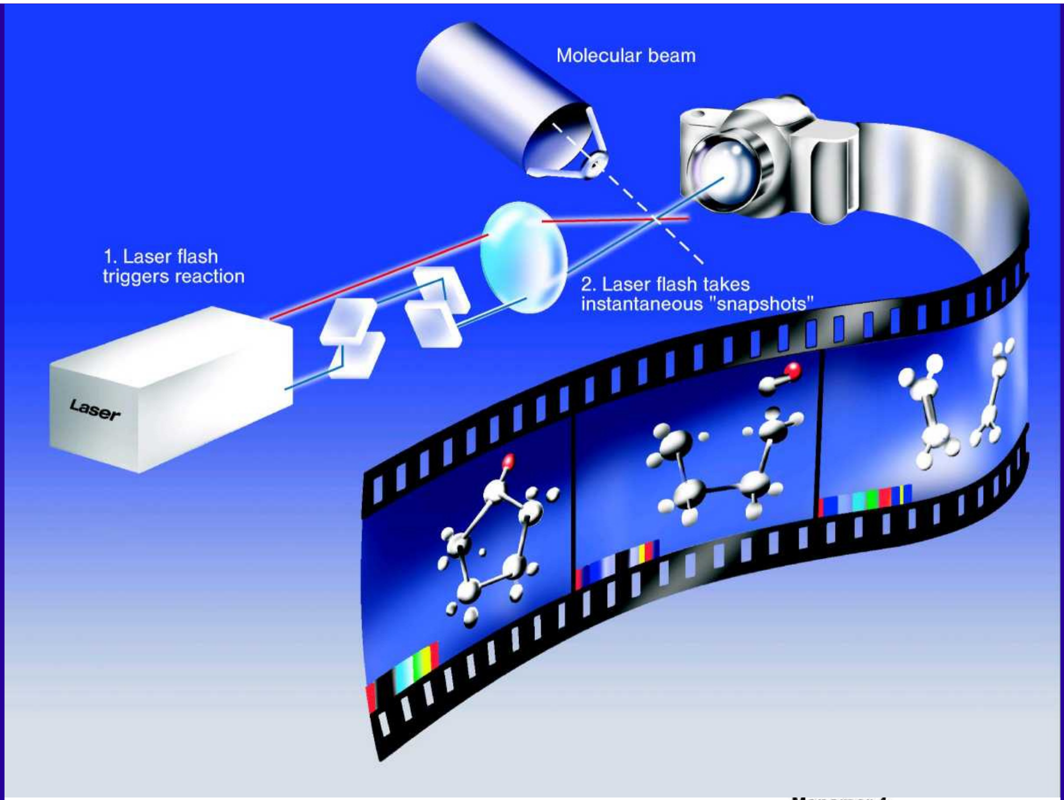
not to scale

X-Ray Free - Electron Laser XFEL

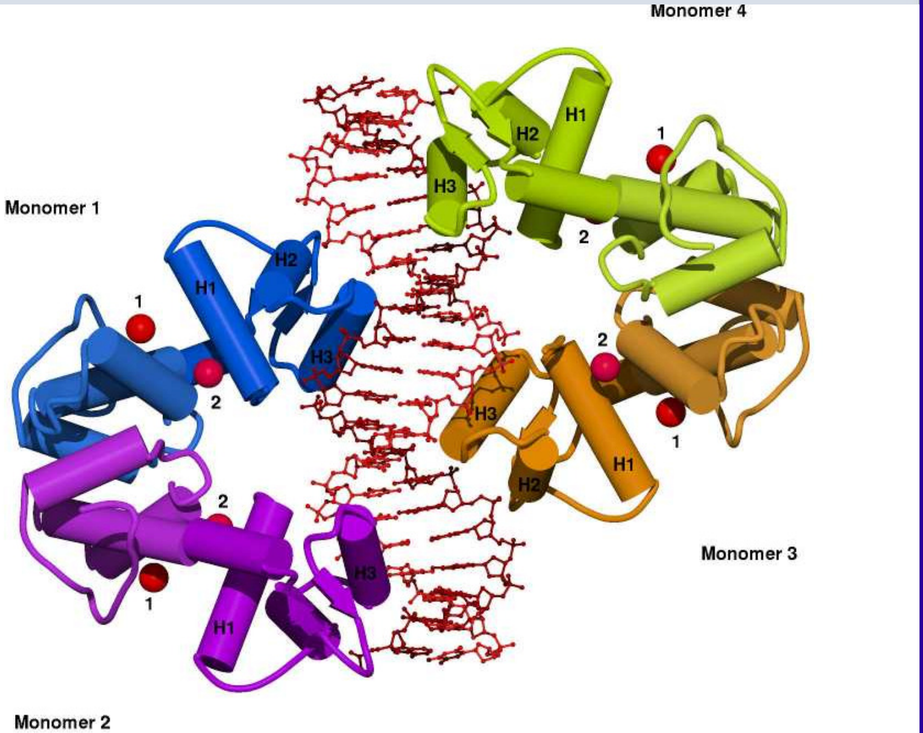




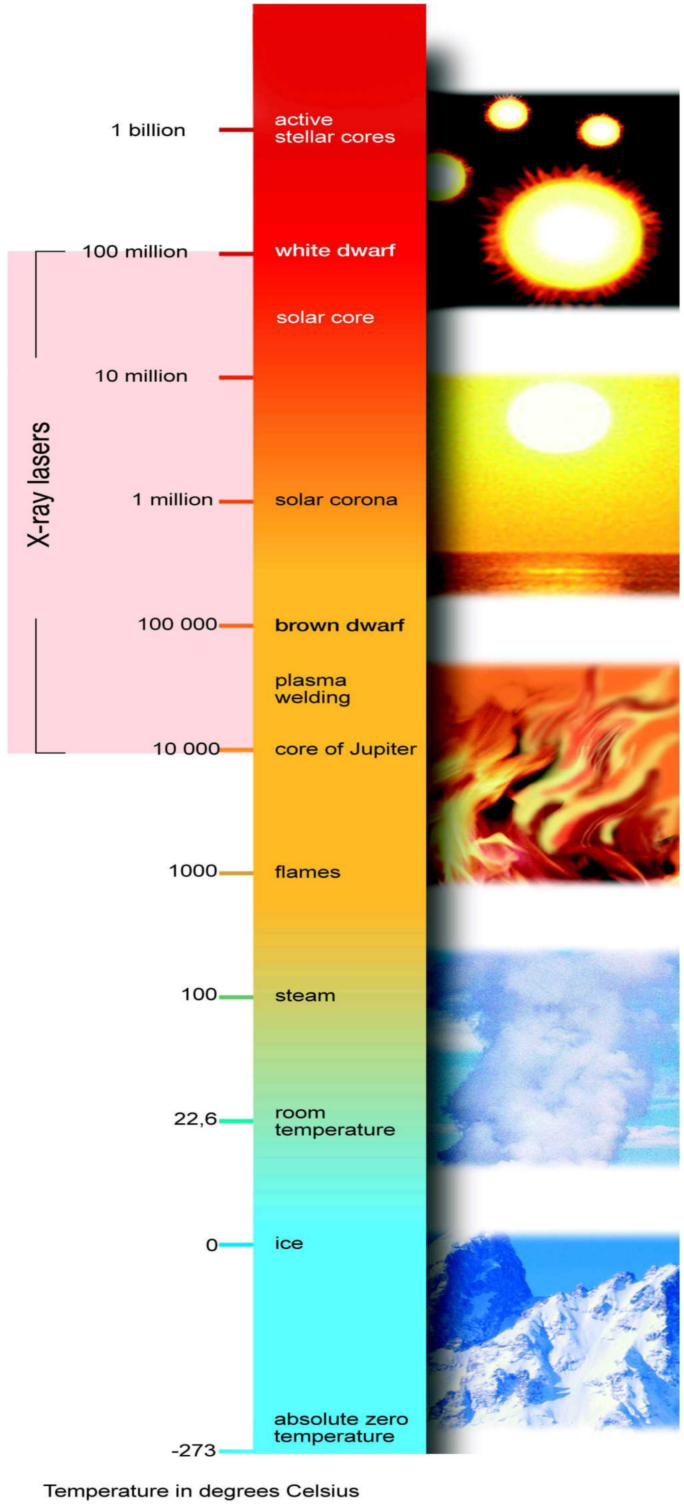
P. Gürtler, HASYLAB, Oct 02
Peak Brilliance [Phot./(sec · mrad² · mm² · 0.1% bandw.)]
Energy [eV]
TESLA SASE FELs
DESY TTF-FEL (seeded)
LCLS
DESY TTF-FEL
measured September 2001
Spontaneous Spectrum SASE FEL 1
20 GeV
10 GeV
Spontaneous Spectrum SASE FEL 2
TESLA spontaneous Undulator
SPring8 Undulator (30m in vacuum)
ESRF-Undulator (ID23)
TTF-FEL spontan
BESSY-II U-49
APS Undulator (Typ A)
BESSY-II U-125
PETRA Undulator
ALS U5.0



Molecular beam
1. Laser flash triggers reaction
2. Laser flash takes instantaneous "snapshots"
Laser



Monomer 4
Monomer 1
Monomer 3
Monomer 2
H1
H2
H3
1
2



1 billion
active stellar cores
100 million
white dwarf
solar core
10 million
X-ray lasers
1 million
solar corona
100 000
brown dwarf
plasma welding
10 000
core of Jupiter
1000
flames
100
steam
22,6
room temperature
0
ice
-273
absolute zero temperature
Temperature in degrees Celsius

Accelerator Driven Sub-critical Reactor System (ADS)

Fuel : U238 Thorium or nuclear waste

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1. **High power proton accelerator (Energy & Current)**

   1 GeV, > 10 mA , CW current

   To generate external neutron source ~ 10^{18} n/s

2. **Spallation target - heavy element (Pb, Pb-Bi, W etc)**

   for > 10 MW beam power

3. **Normal Power Reactor - thermal or fast,**

   except : core is sub-critical (K_{eff} ~ 0.95-0.98)

Accelerators running in the world

CATEGORY OF ACCELERATORS	NUMBER IN USE (*)
High Energy acc. (E >1GeV)	~120
Synchrotron radiation sources	>100
Medical radioisotope production	~200 } 9000
Radiotherapy accelerators	> 7500 } 9000
Research acc. included biomedical research	~1000 } 9000
Acc. for industrial processing and research	~1500
Ion implanters, surface modification	>7000
TOTAL	> 17500

(*) W. Maciszewski and W. Scharf: Int. J. of Radiation Oncology, 2004

- About half are used for bio-medical applications

Cancer Stages

Local Tumor

Regional Metastasis

Systemic Disease

Cancer Treatment

Surgery

Radiation Therapy

ChemoTherapy

ImmunoTherapy

Hadron Therapy

Radiation Therapy using strongly interacting particles

- Neutrons
- Protons
- Pions
- Ions (alpha, Carbon, Ne)

Proton & Neutron Therapy address deficiencies in photon therapy

- Protons: better dose distributions
- Neutrons: better tumor killing

Ref: Petti and Lennox, Hadronic Radiotherapy,
Ann. Rev. Nuclear & Particle Science, 1994. 44:154-197.

Proton Therapy

30 centers worldwide — 65,000 patients

+ 12 EU
  5 US
  2 Taiwan
  } constructing / planned

Heavy Ion / Carbon — 8,000 patients

3 — Chiba, Japan
Hyogo, Japan
Germany

+ 5 EU
  1 Taiwan
  } constructing / planned

Neutron Therapy — 11,000 patients

Fermi Lab
Detroit
Seattle
South Africa

Neutron Therapy

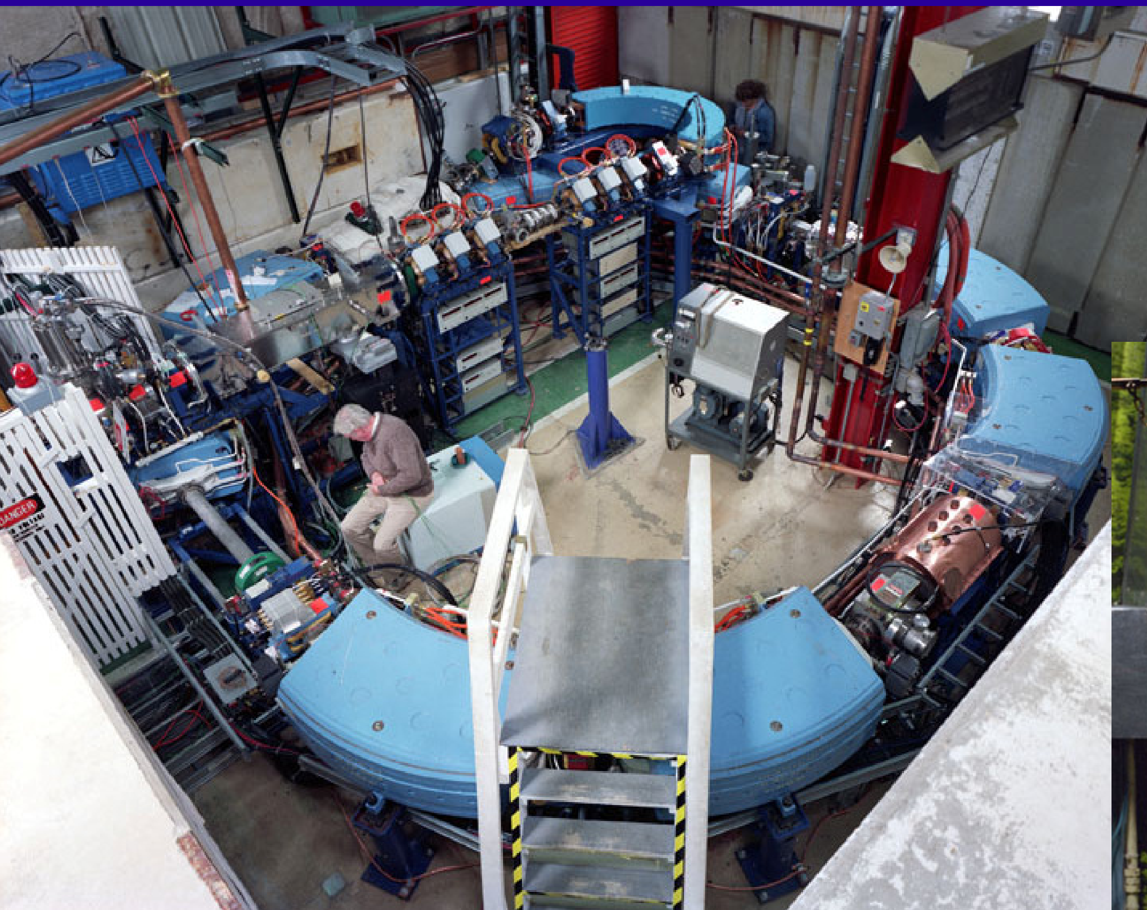
Seattle

Detroit
Harper MSU-NSCL

iThemba
South
Africa

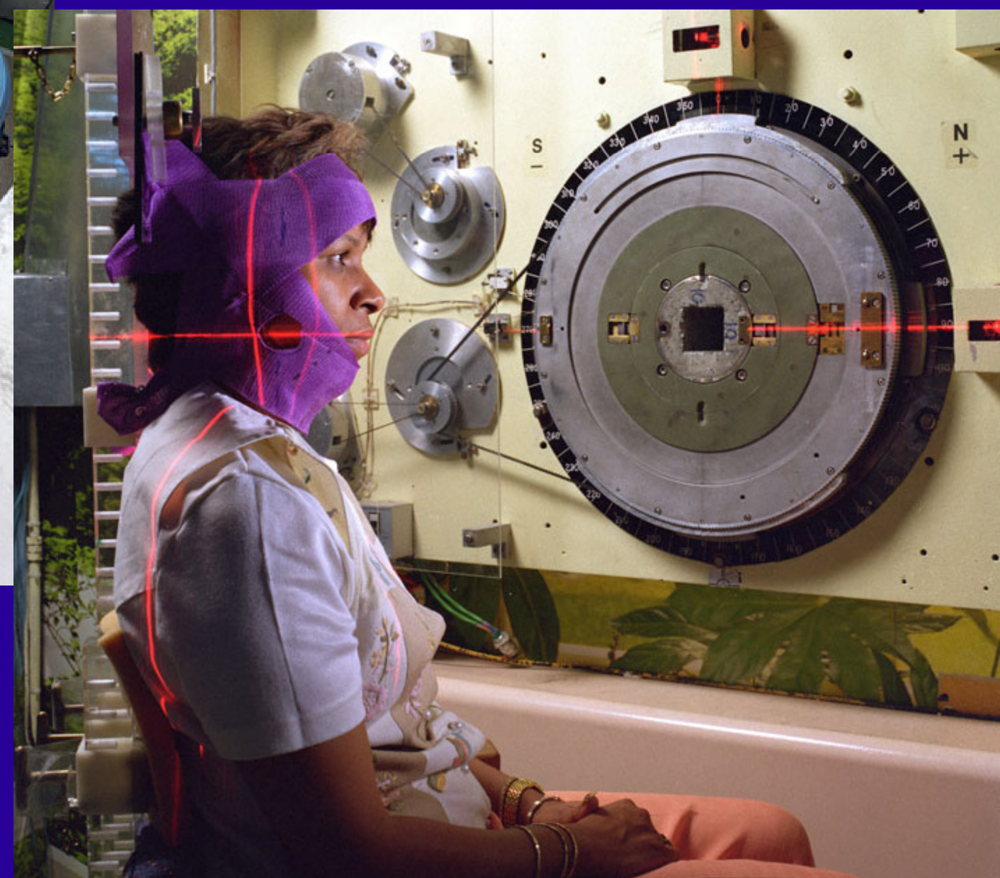
Proton Therapy

built by Fermi Lab



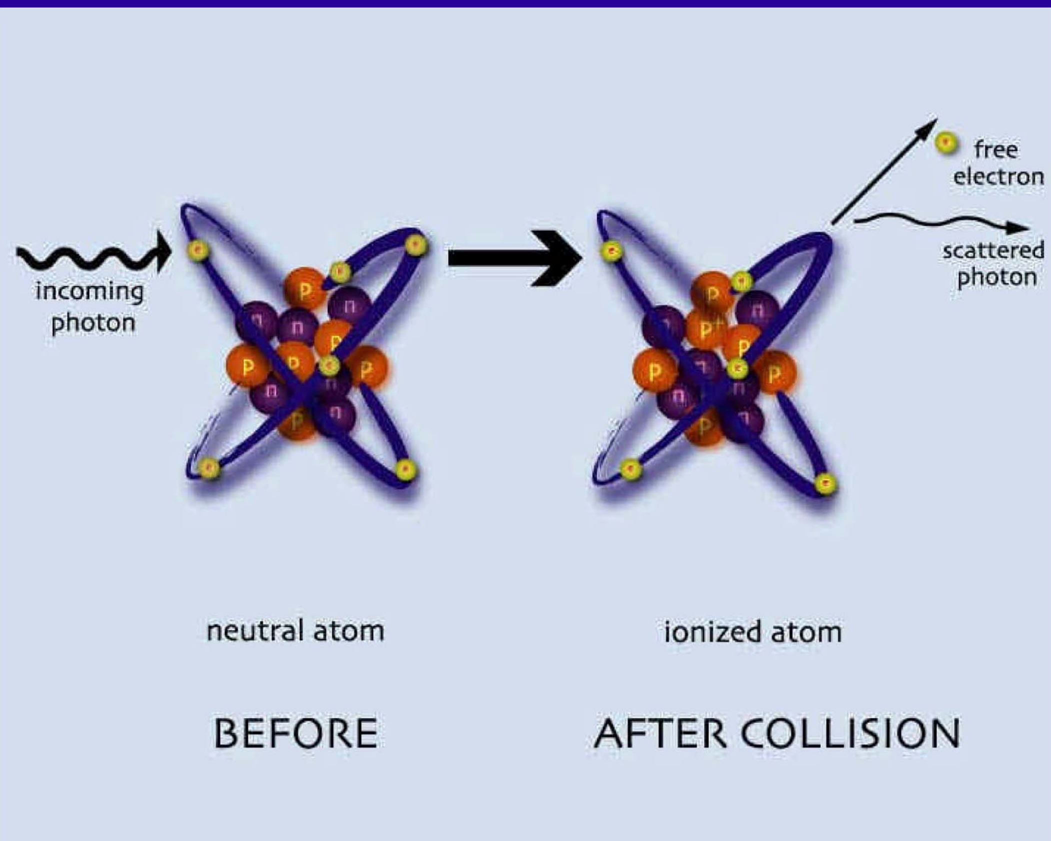
Neutron Therapy

Fermi Lab

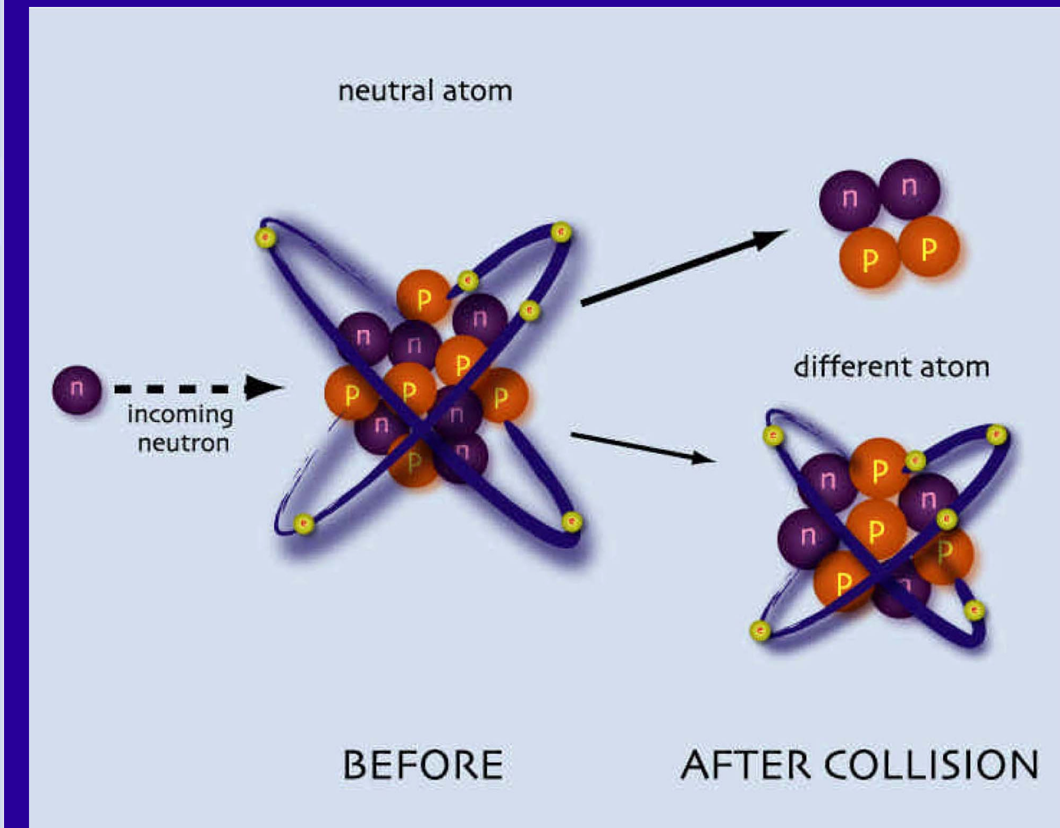


Linear Energy Transfer (LET)

Low LET



High LET



Protons & photons

low LET

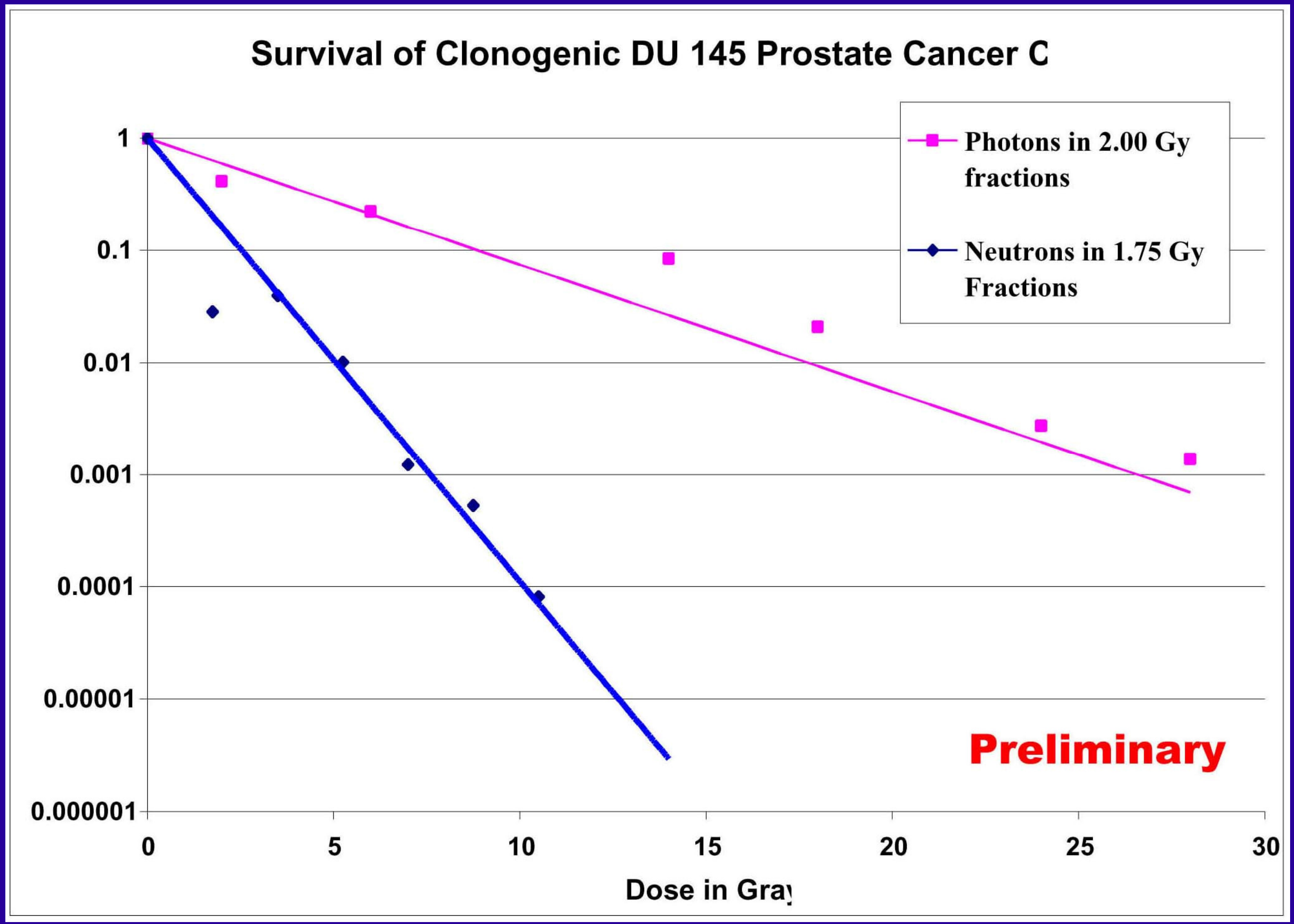
similar biological effectiveness

Neutrons & Ions

high LET

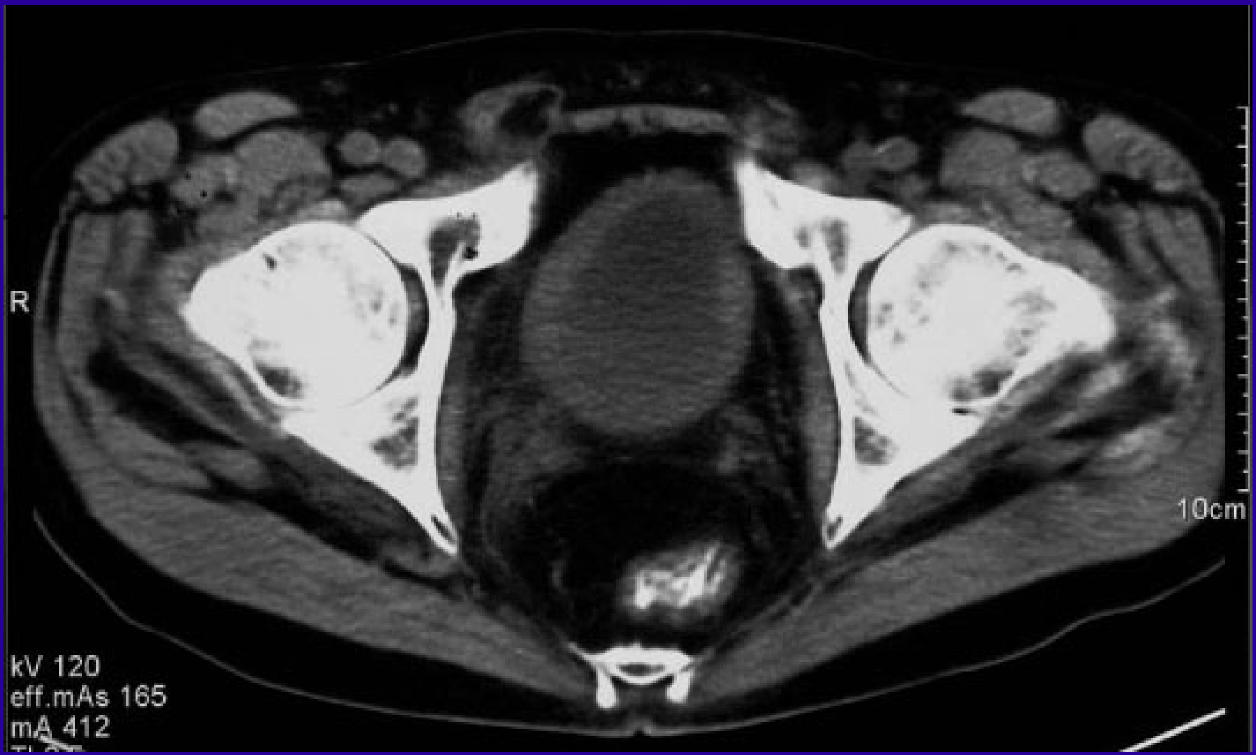
high Relative Biological Effectiveness (RBE)

Fermilab 66 MeV Neutrons
RBE = 4 for Prostate Cancer



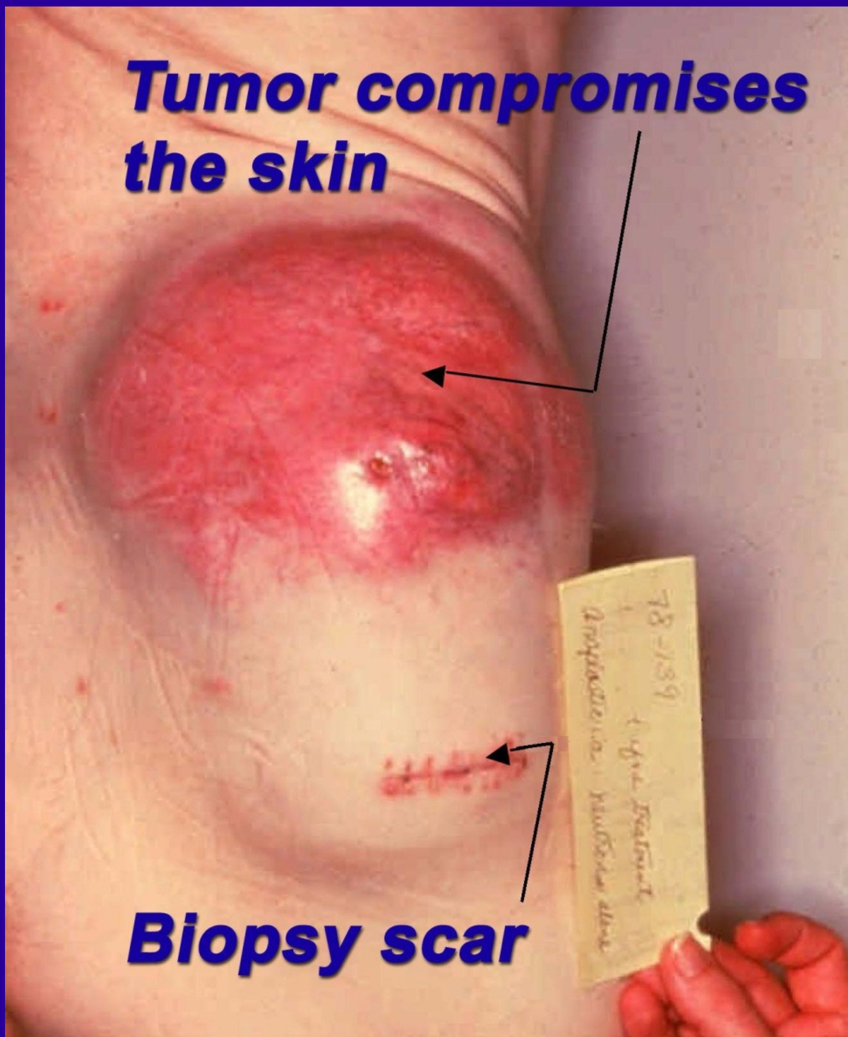
Blazek, Urbon, Lennox, Kroc, Pientak

Before Neutron Therapy

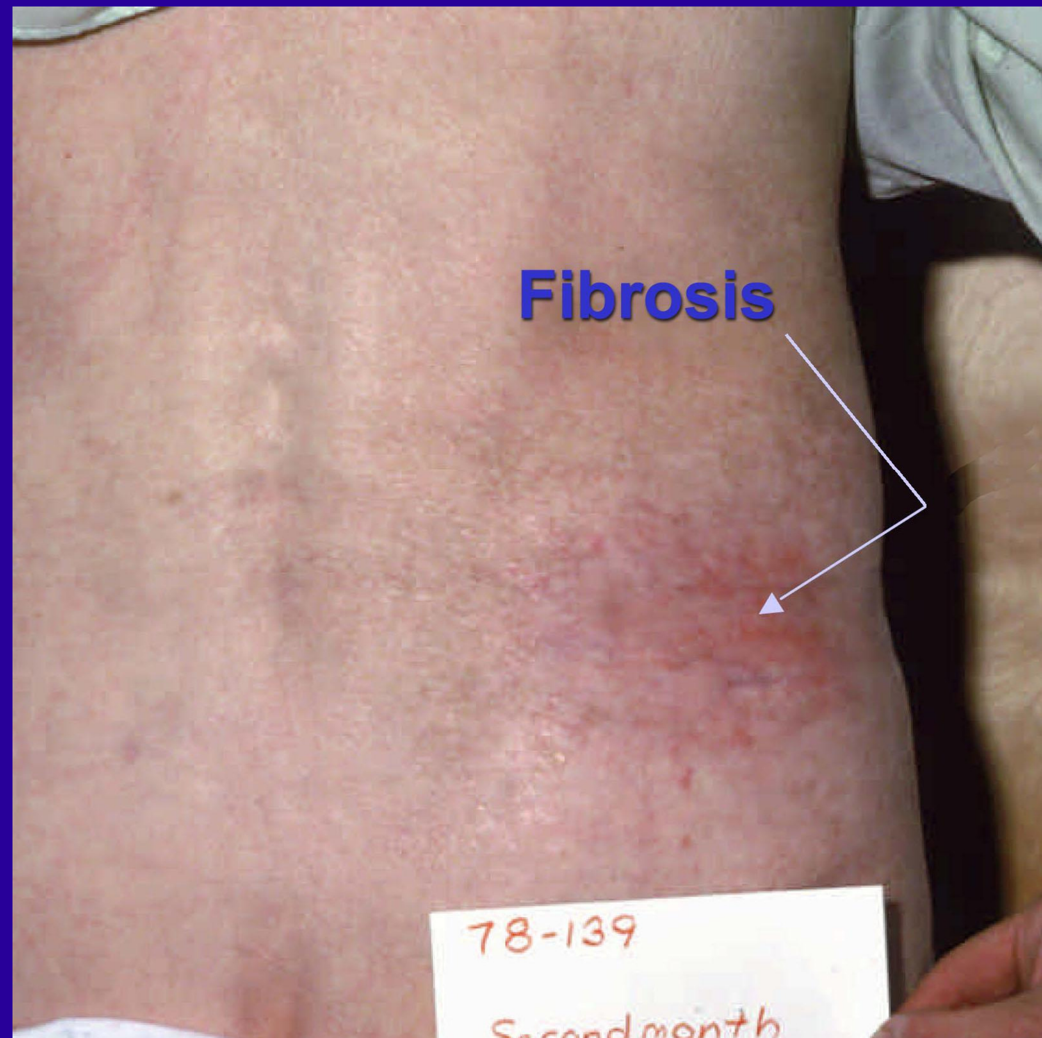


After 7 Treatments
12.25 Gy of Neutrons

Inoperable Soft-tissues Sarcoma



Two-months follow-up after the End of Neutron Treatment



Inoperable Neck Tumor before Neutron Therapy

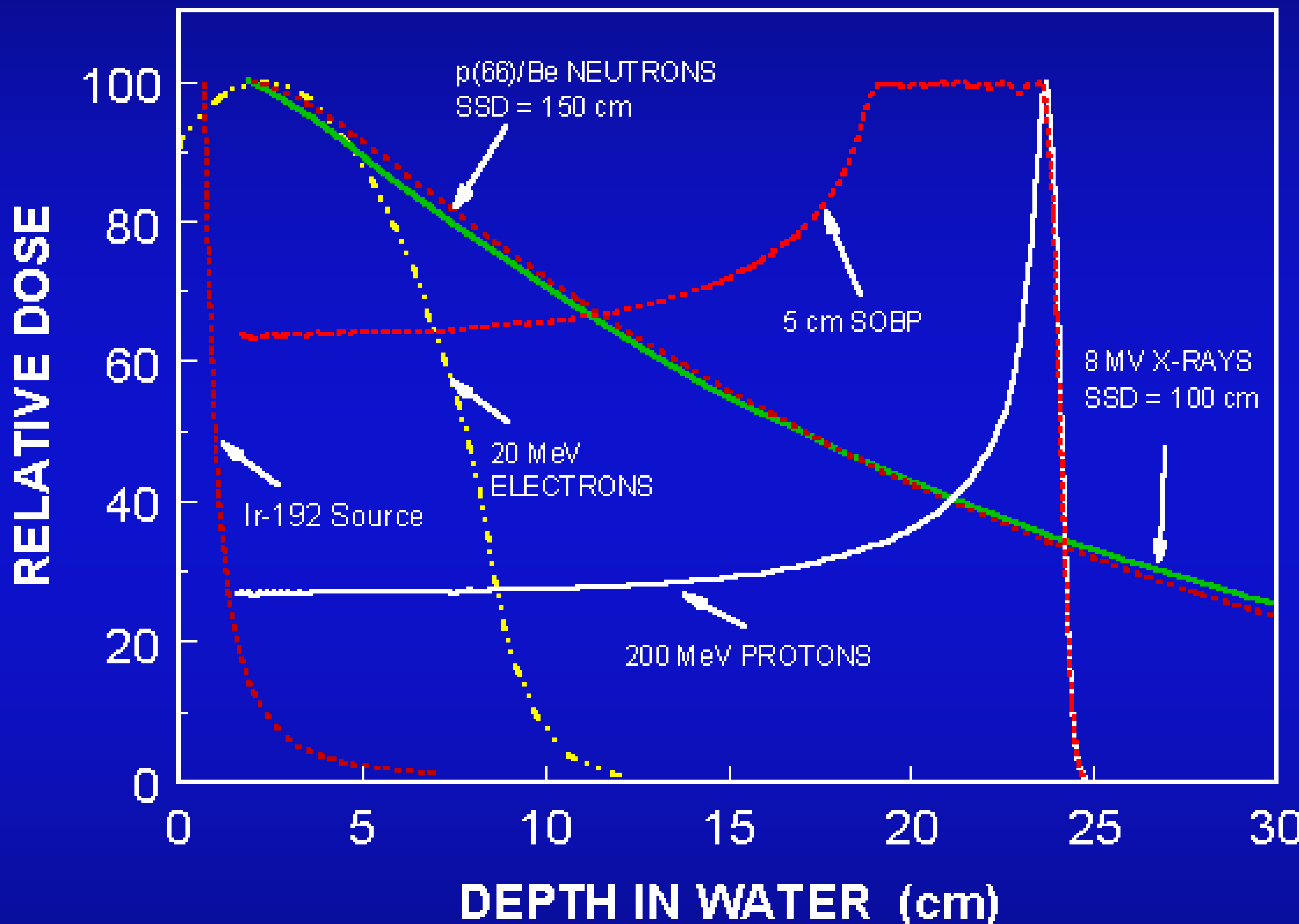
Two Years after Neutron Therapy

Squamous cell carcinoma from snuff chewing

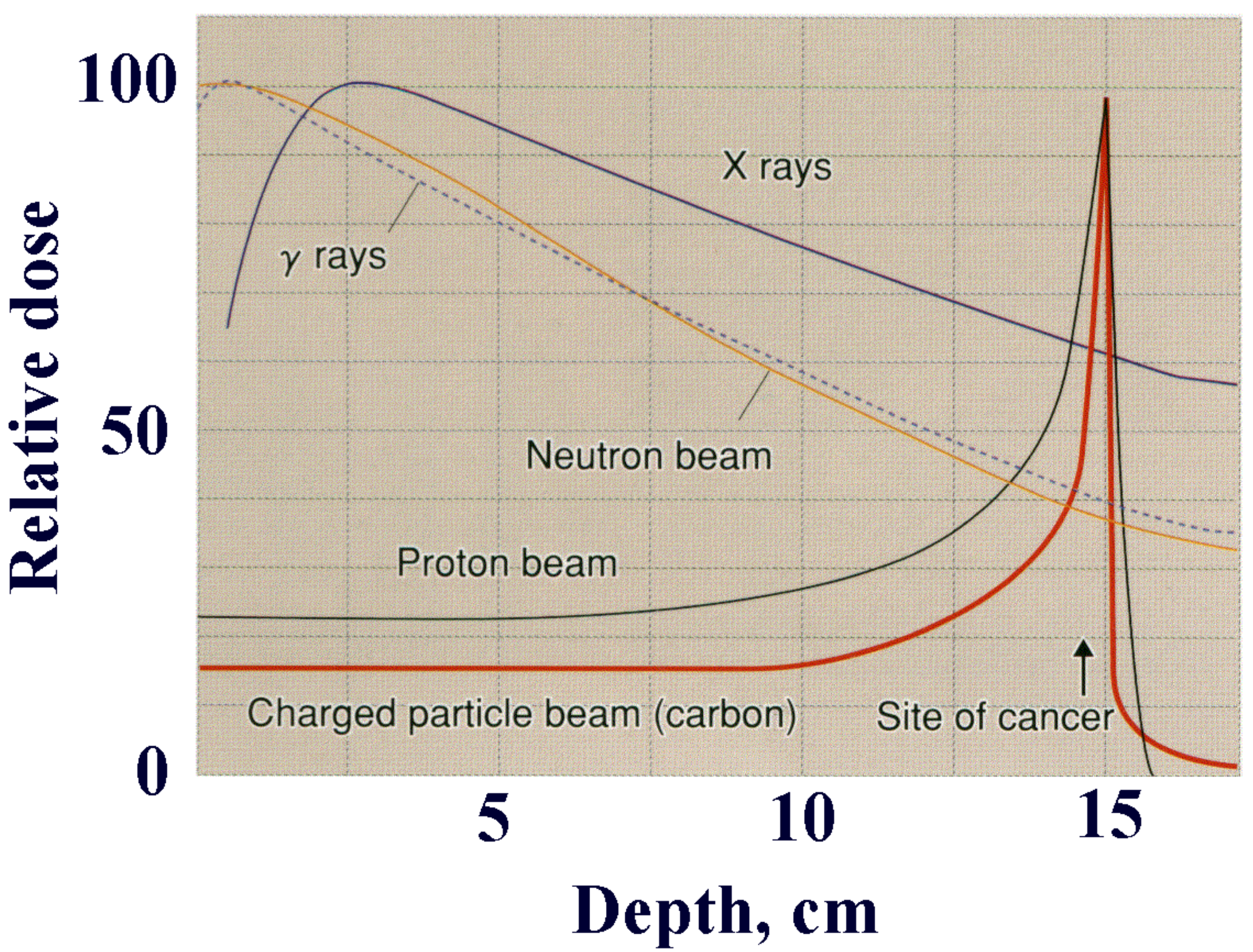
Loma Linda
Proton Therapy

1,000 patients / year

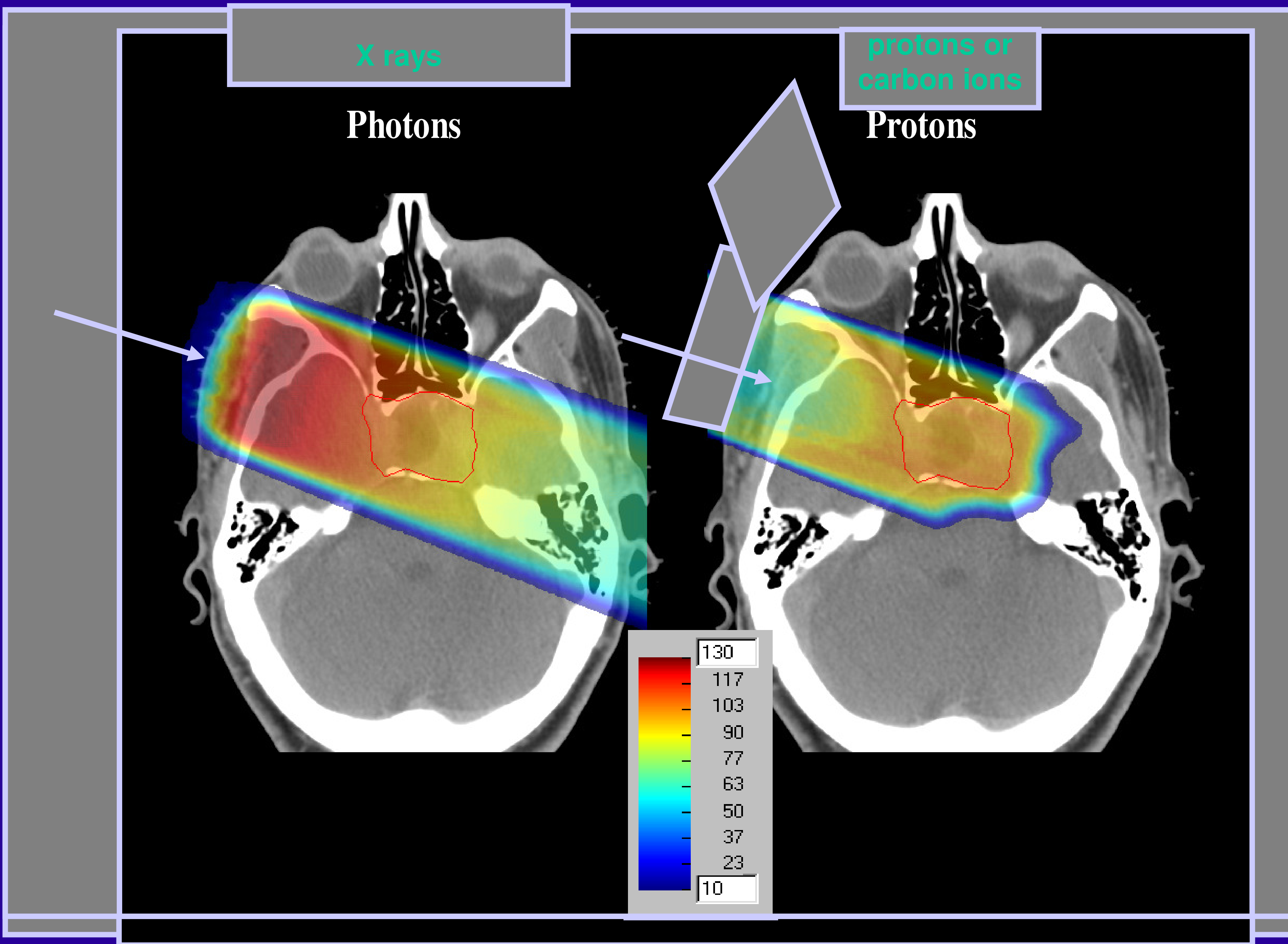
Radiation Dose vs. Depth



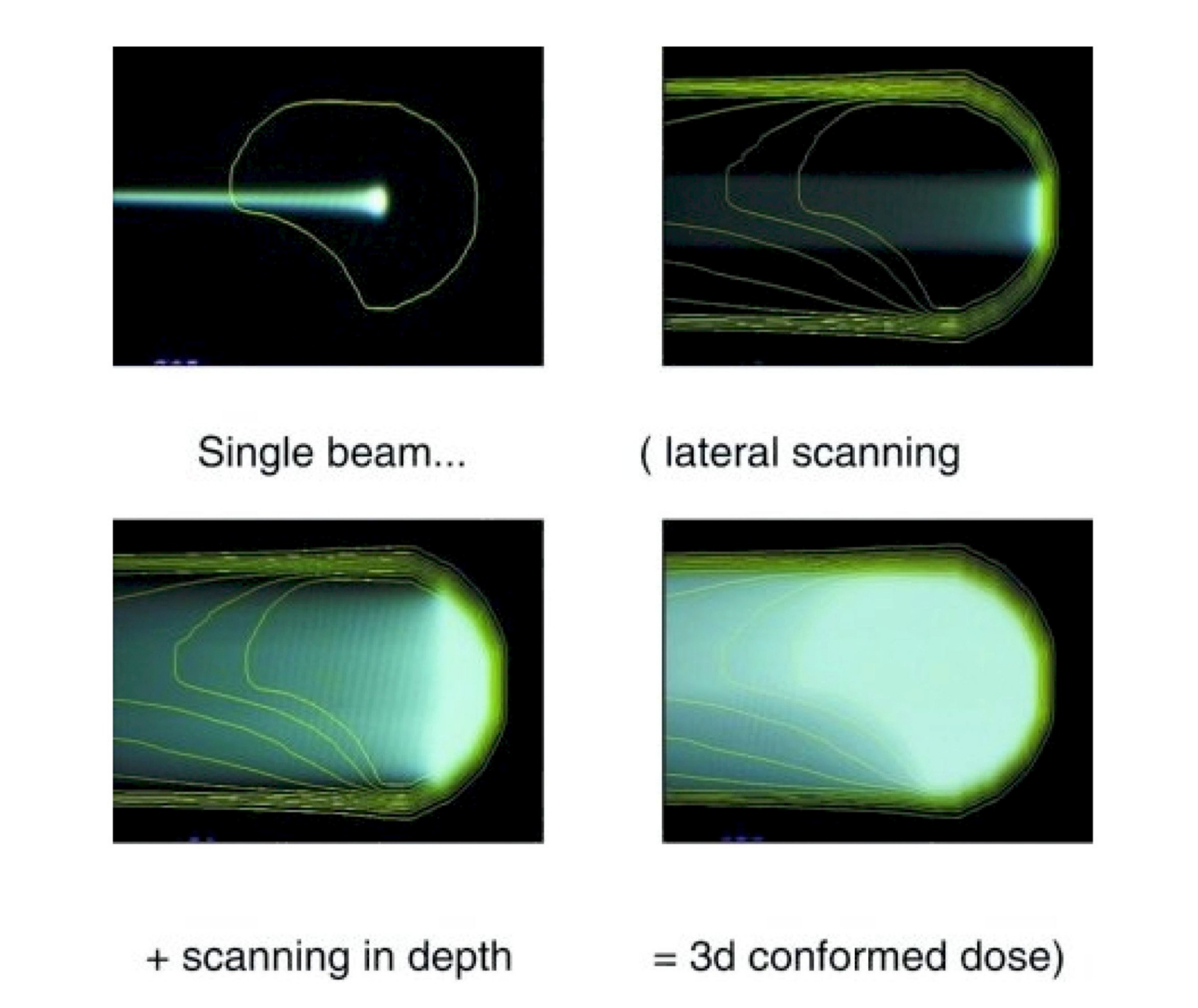
Heavy Ion Therapy (Carbon)



- Narrow Bragg peak
- High RBE Relative Biological Effectiveness
- Small lateral scattering


X rays
protons or carbon ions
Photons
Protons
130
117
103
90
77
63
50
37
23
10

Active scanning – much improved 3-D conformal dose



(Patient treatment demos courtesy of PSI)

Proton Therapy

Benign Tumors
Acoustic neuroma
Arteriovenous malformation
Craniopharyngioma
Pituitary adenoma
Intracranial meningioma

Pediatric Malignancies
Medulloblastoma, craniospinal
Ependymoma
Pineal tumors
Astrocytoma
Retinoblastoma
Orbital rhabdomyosarcoma

Ophthalmological Conditions
Malignant/benign tumors of the orbit
Ocular (uveal) melanoma

Lung Cancer
Early-stage, medically inoperable lung cancer

Head and Neck Malignancies
Nasopharyngeal carcinoma
Paranasal sinus carcinoma
Oropharyngeal/parapharyngeal malignancies

Base of Skull Sarcomas
Chordoma and chondrosarcoma

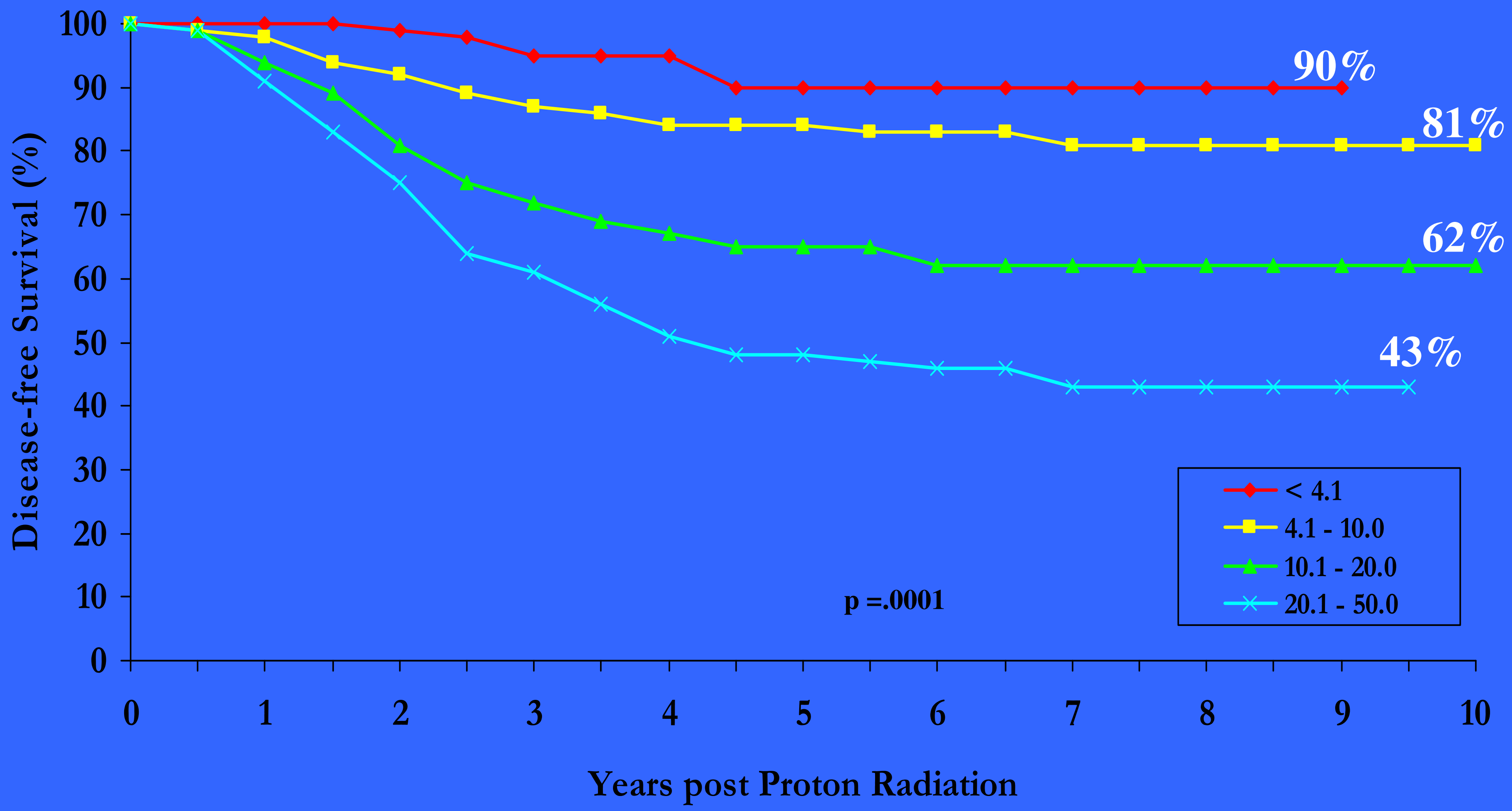
Spinal Cord and Paraspinal Tumors
Paraspinal soft-tissue malignancies
Chordoma
Sarcoma subtypes

Gastrointestinal Malignancies
Carcinoma of the rectum
Pancreatic carcinoma
Hepatocelluar carcinoma

Genitourinary Cancer
Bladder carcinoma
Prostate malignancies

Prostate Cancer

Effect of Initial PSA on Disease-free Survival



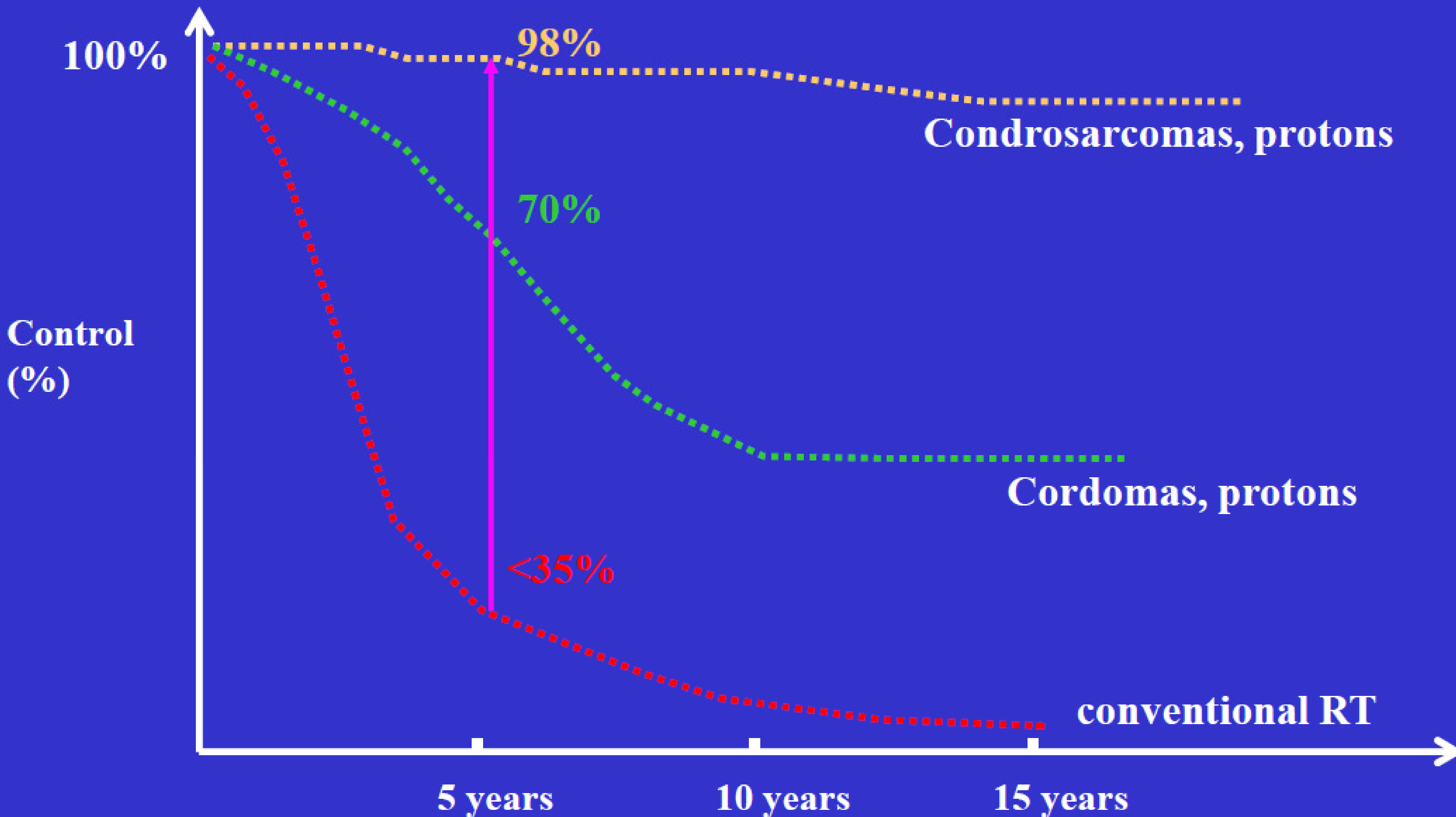
Prostate Cancer

10 year Disease-free Survival

Stage T1 - T2

Pretreatment PSA	Radical Prostatectomy Johns Hopkins* 2123 pts	Protons 74-75 Gy LLUMC 1102 pts
≤ 4.0	91%	92%
4.1 – 10.0	79%	81%
10.1 – 20.0	57%	64%
> 20.0	48%	53%

*Han, Partin et al.: Urol Clin of N Amer, 2001


100%
98%
Condrosarcomas, protons
70%
Control
(%)
Cordomas, protons
<35%
conventional RT
5 years
10 years
15 years

Early Stage Lung Cancer Tx

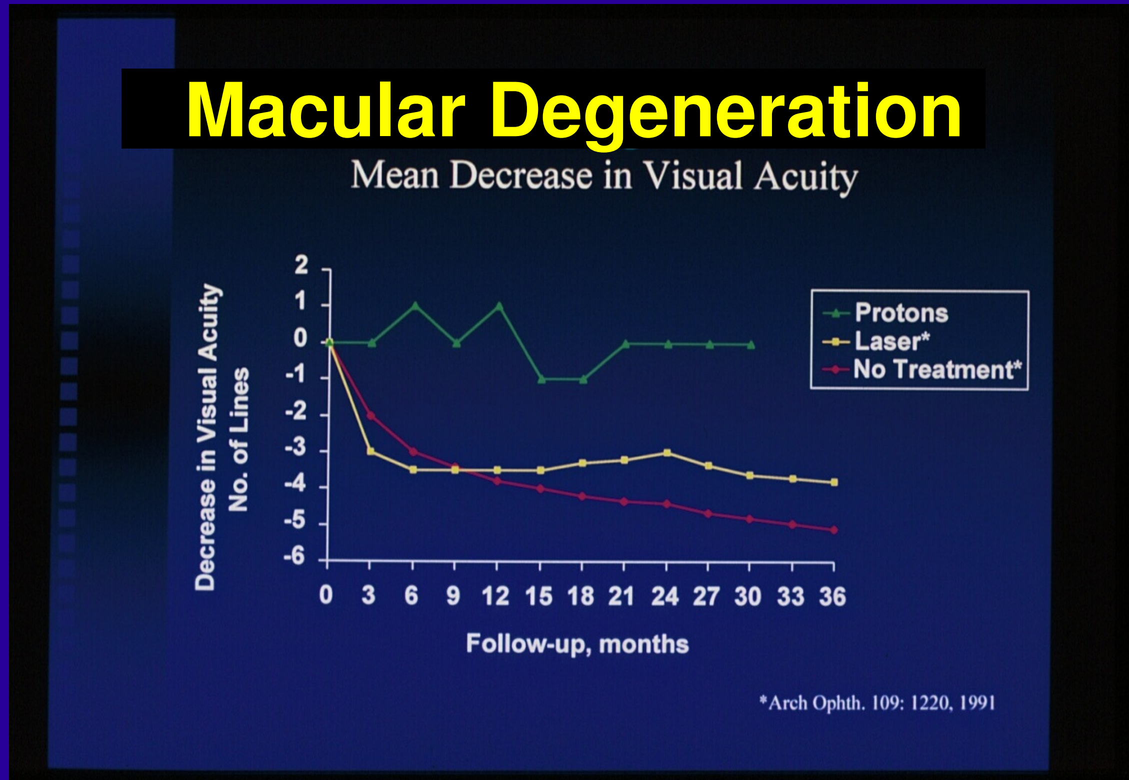
60 Gray in 10 Fractions (46 patients)

	Published X-ray Tx Results	Published LLU Proton Tx Results
3 yr. local control	56%	74%
3 yr. disease free survival	43%	72%
3 yr. overall survival	32%	55%

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 %	

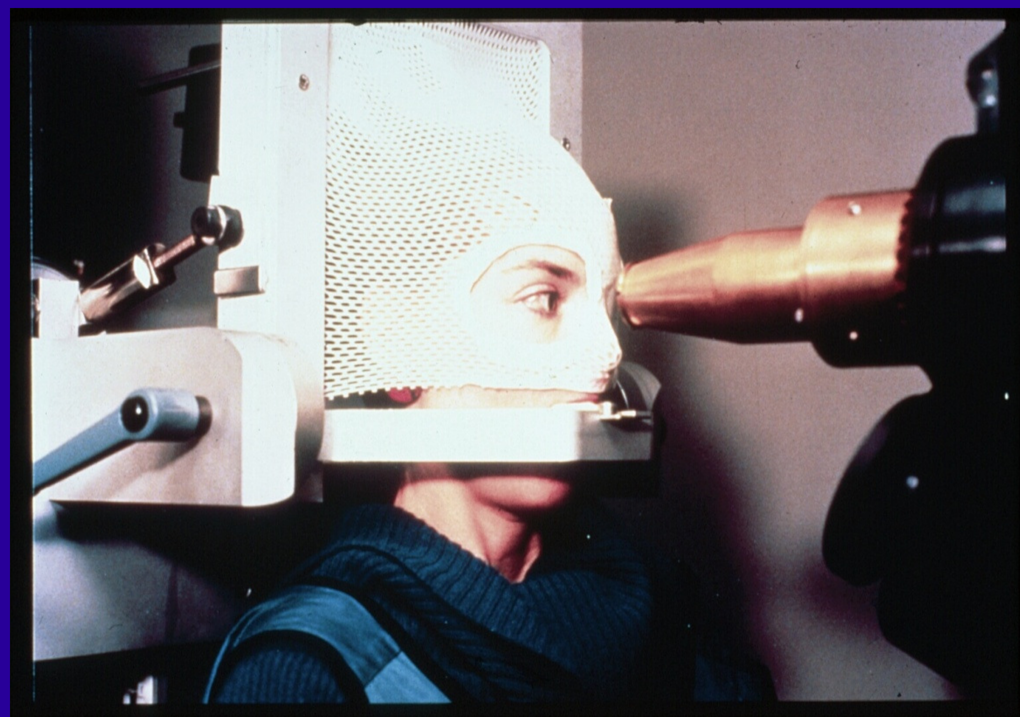
Table by G. Kraft 2007

Results of C ions



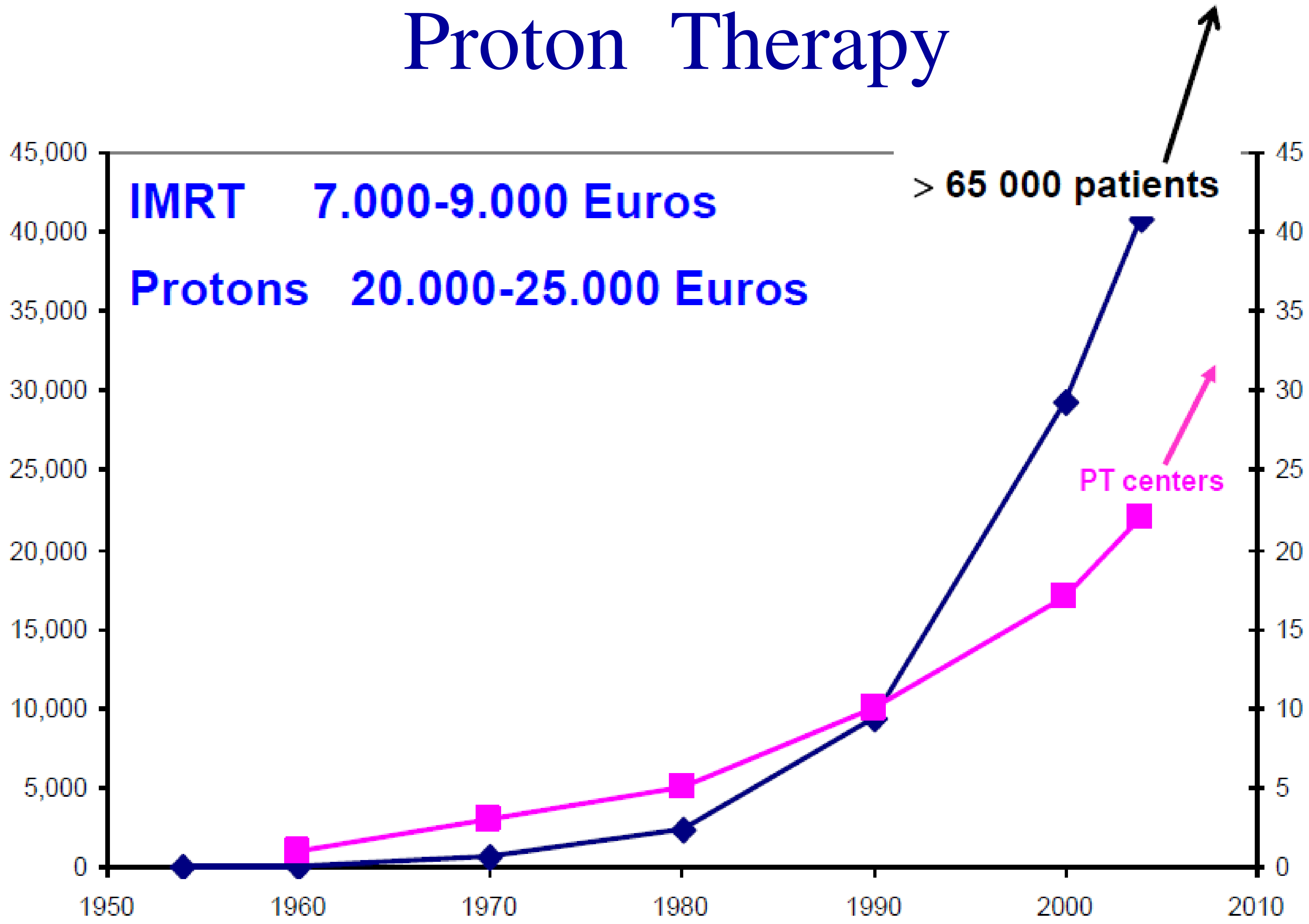
Partial Breast Radiation

-- post lumpectomy

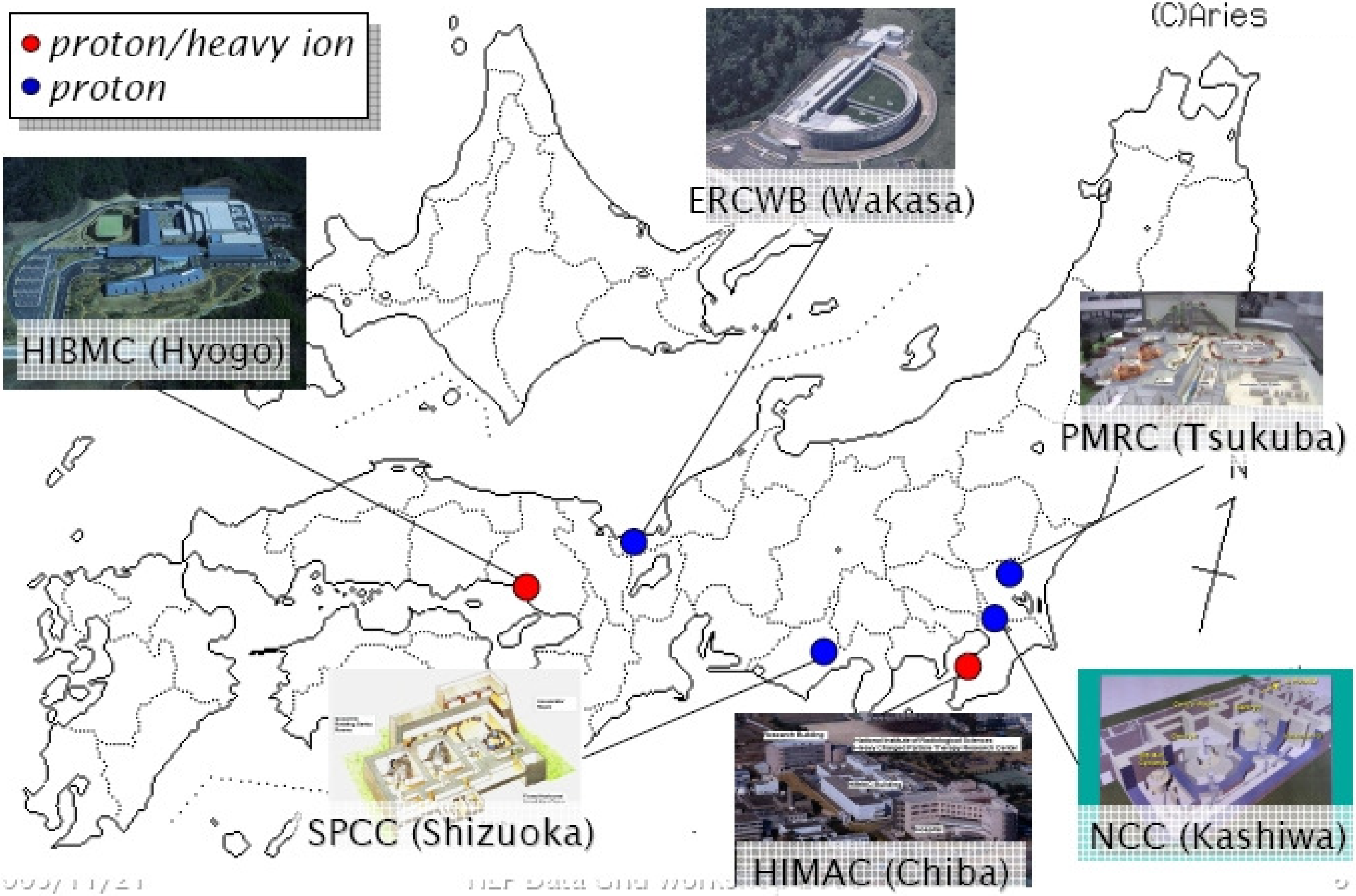


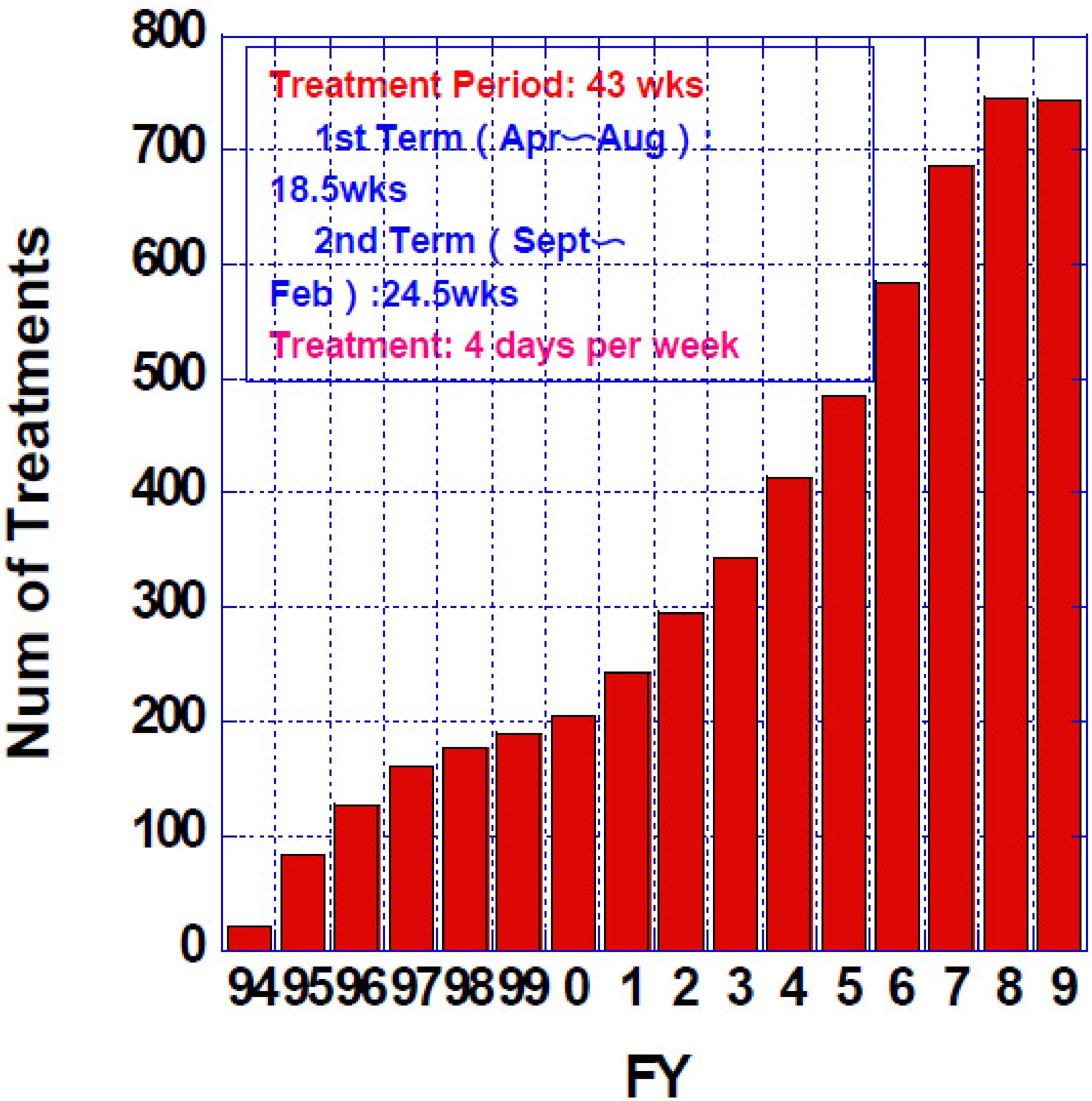
Loma Linda Proton Gantry

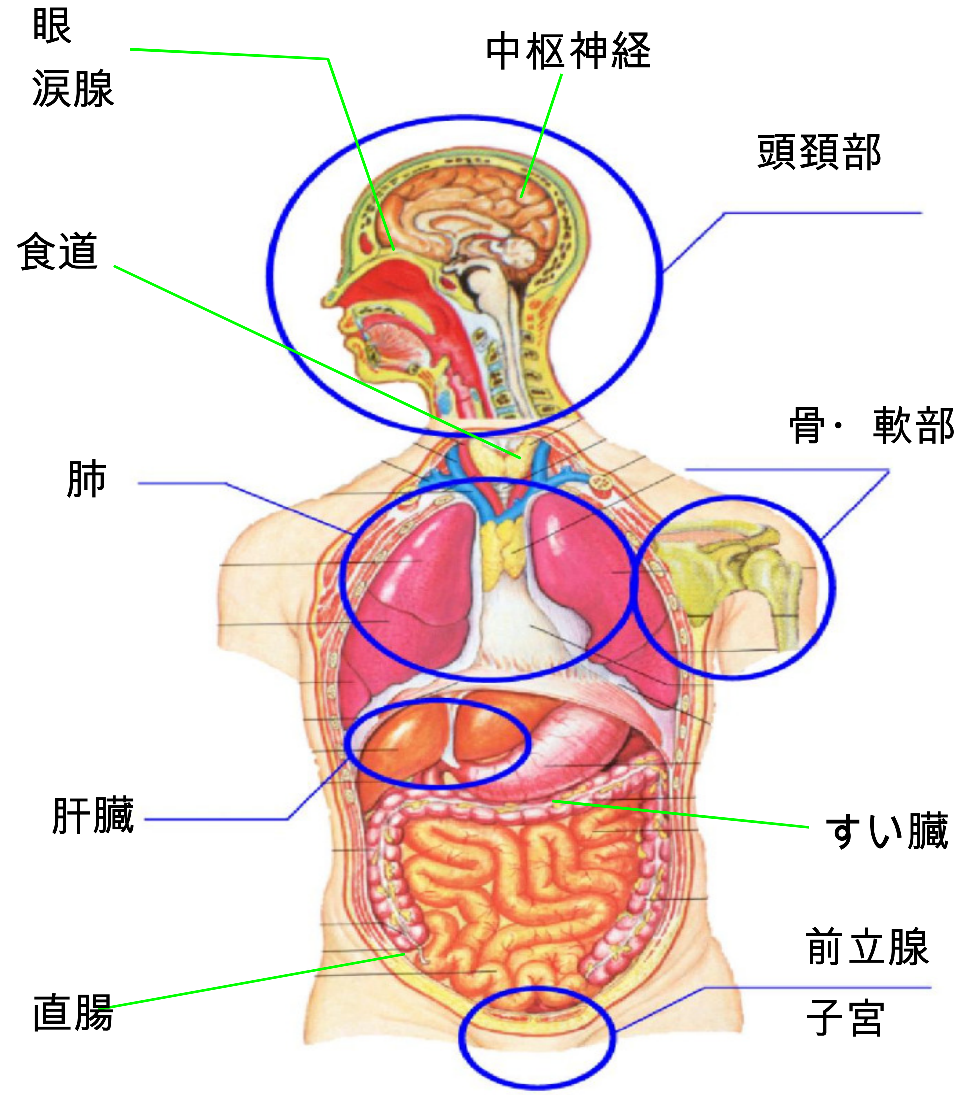
Proton Therapy

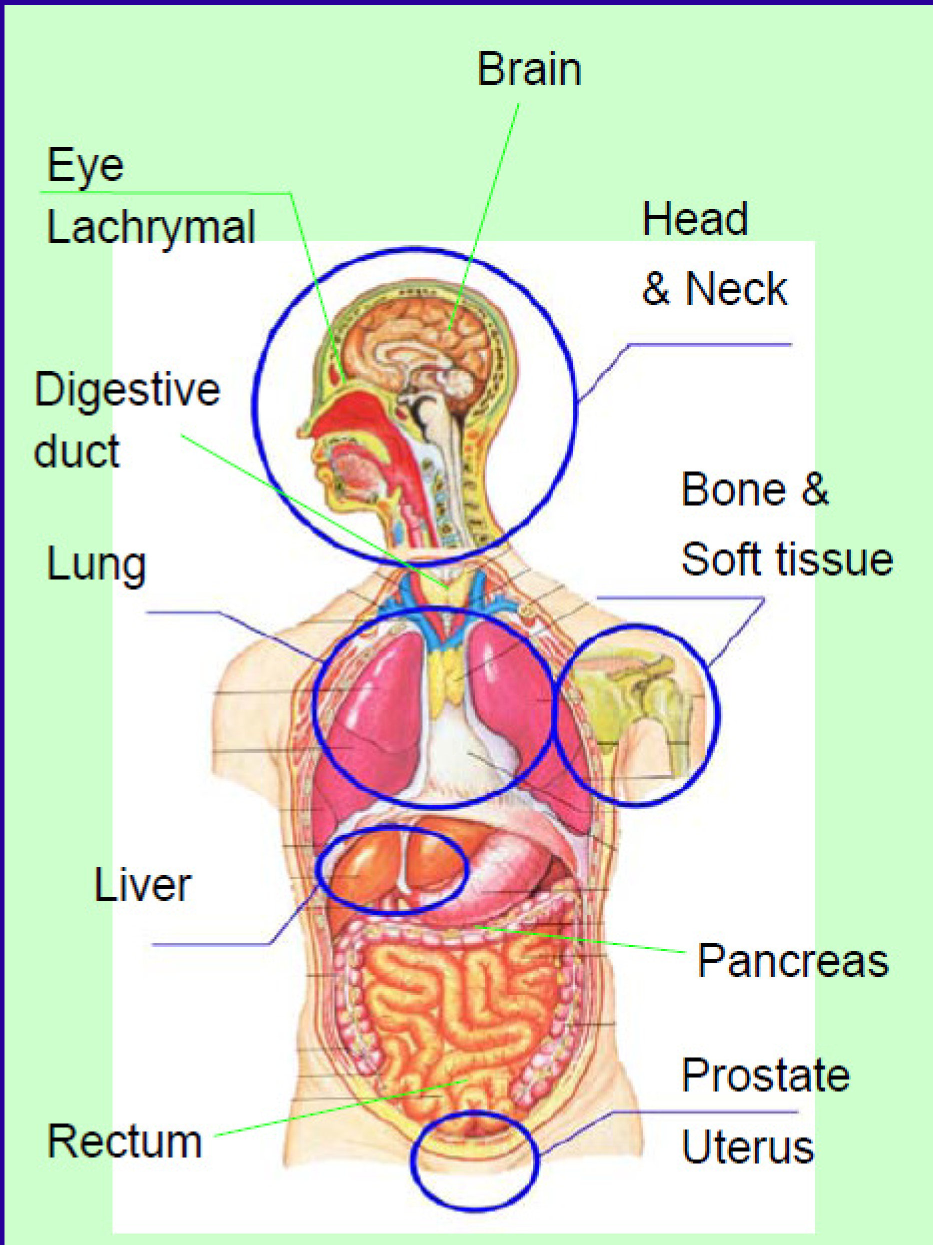


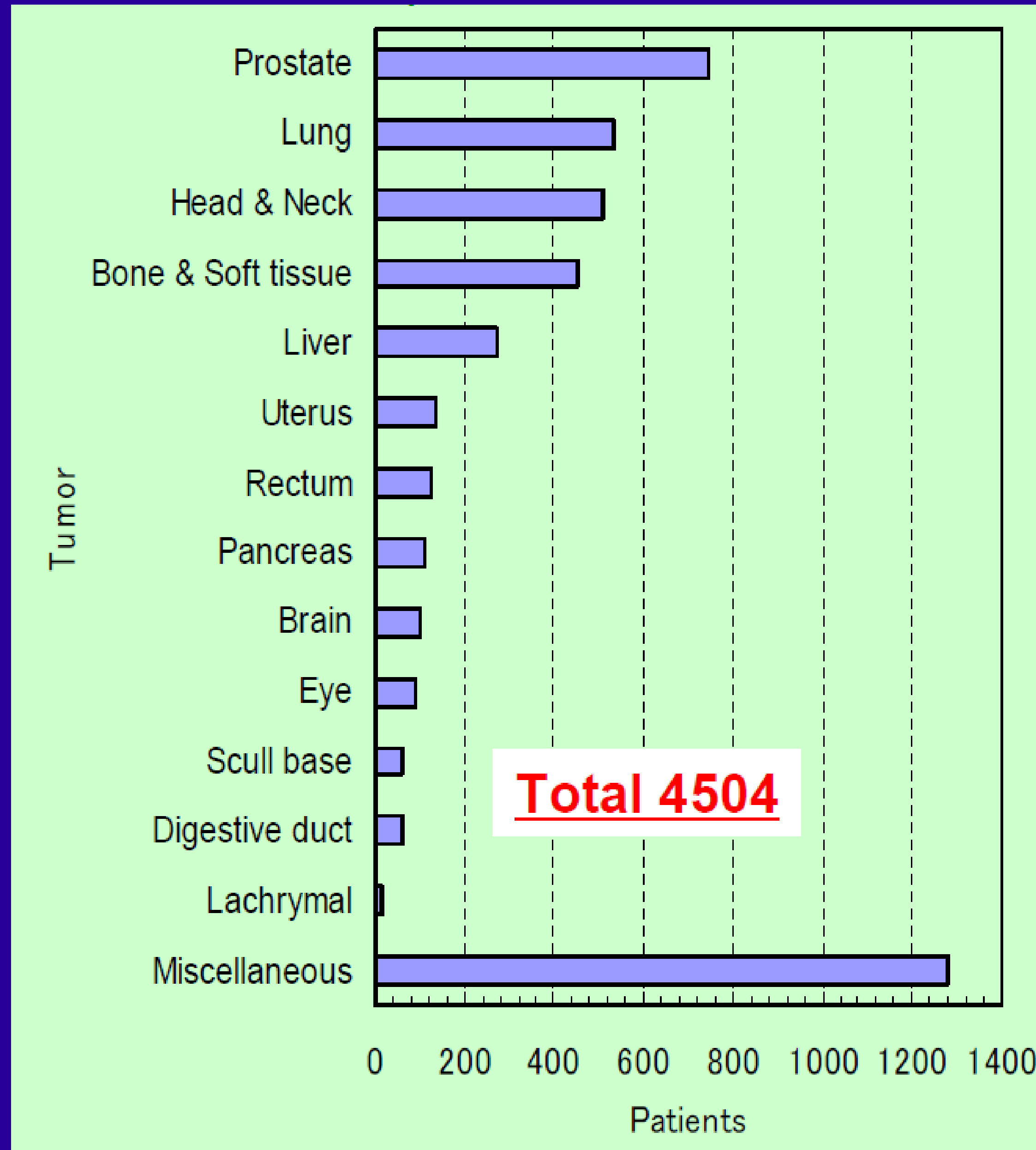
Hadron Therapy Facilities in Japan




Treatment Period: 43 wks
1st Term (Apr～Aug) :
18.5wks
2nd Term (Sept～
Feb) :24.5wks
Treatment: 4 days per week
Num of Treatments
0
100
200
300
400
500
600
700
800
94
95
96
97
98
99
0
1
2
3
4
5
6
7
8
9
FY


眼
涙腺
中枢神経
頭頸部
食道
骨・ 軟部
肺
肝臓
すい臓
前立腺
子宮
直腸


Brain
Eye
Lachrymal
Head
& Neck
Digestive
duct
Bone &
Soft tissue
Lung
Liver
Pancreas
Prostate
Rectum
Uterus


Prostate
Lung
Head & Neck
Bone & Soft tissue
Liver
Uterus
Rectum
Pancreas
Brain
Eye
Scull base
Digestive duct
Lachrymal
Miscellaneous
Tumor
0
200
400
600
800
1000
1200
1400
Patients
Total 4504

Carbon & Proton Hyogo

RPTC, Munich

Numbers of potential patients

From studies in Austria, France, Germany and Italy

X-ray therapy

every 10 million inhabitants 20'000 pts/year

Proton therapy

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

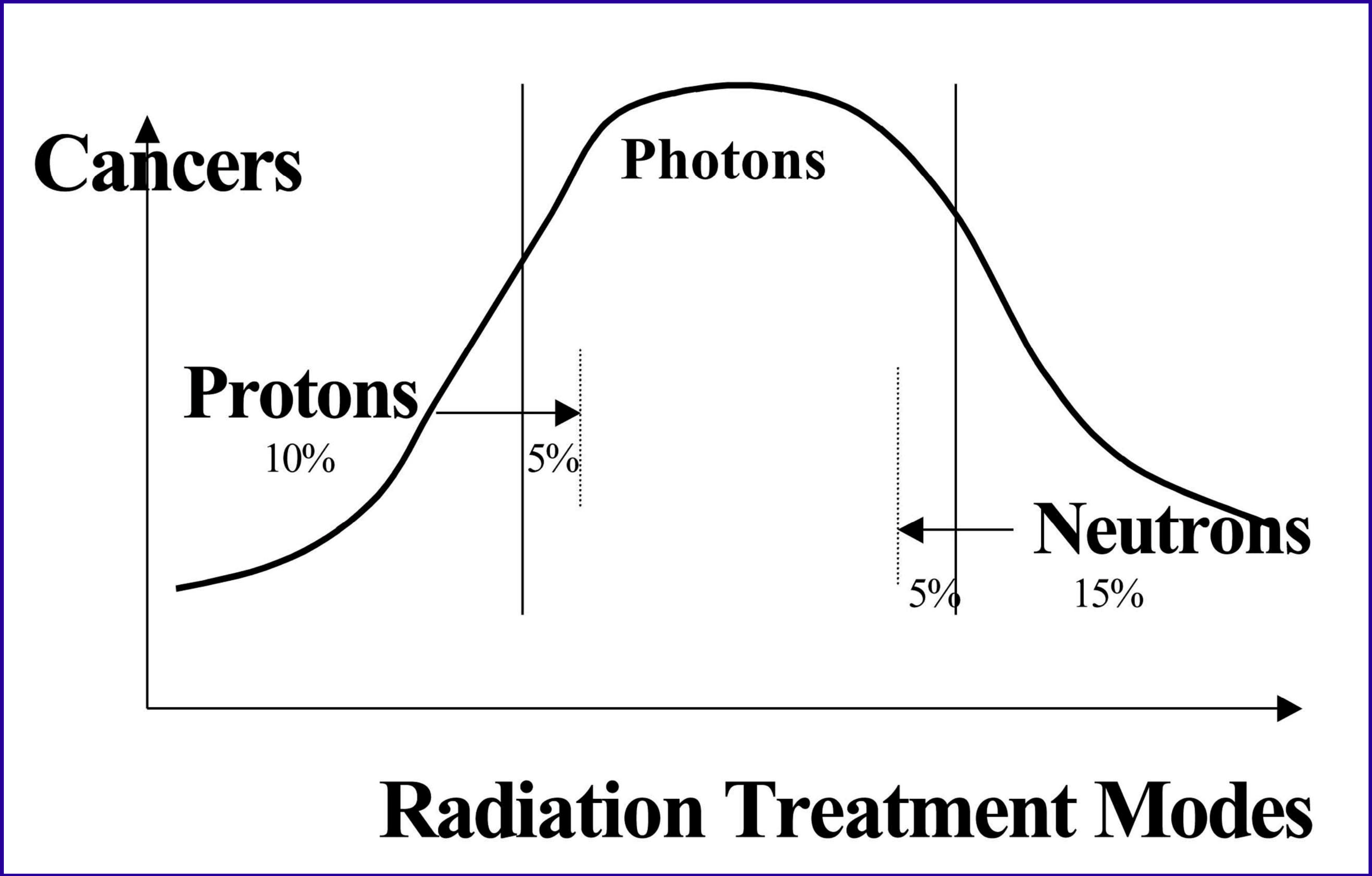
Therapy with **Carbon ions** for radio-resistant tumour

3% of X-ray patients 600 pts/year

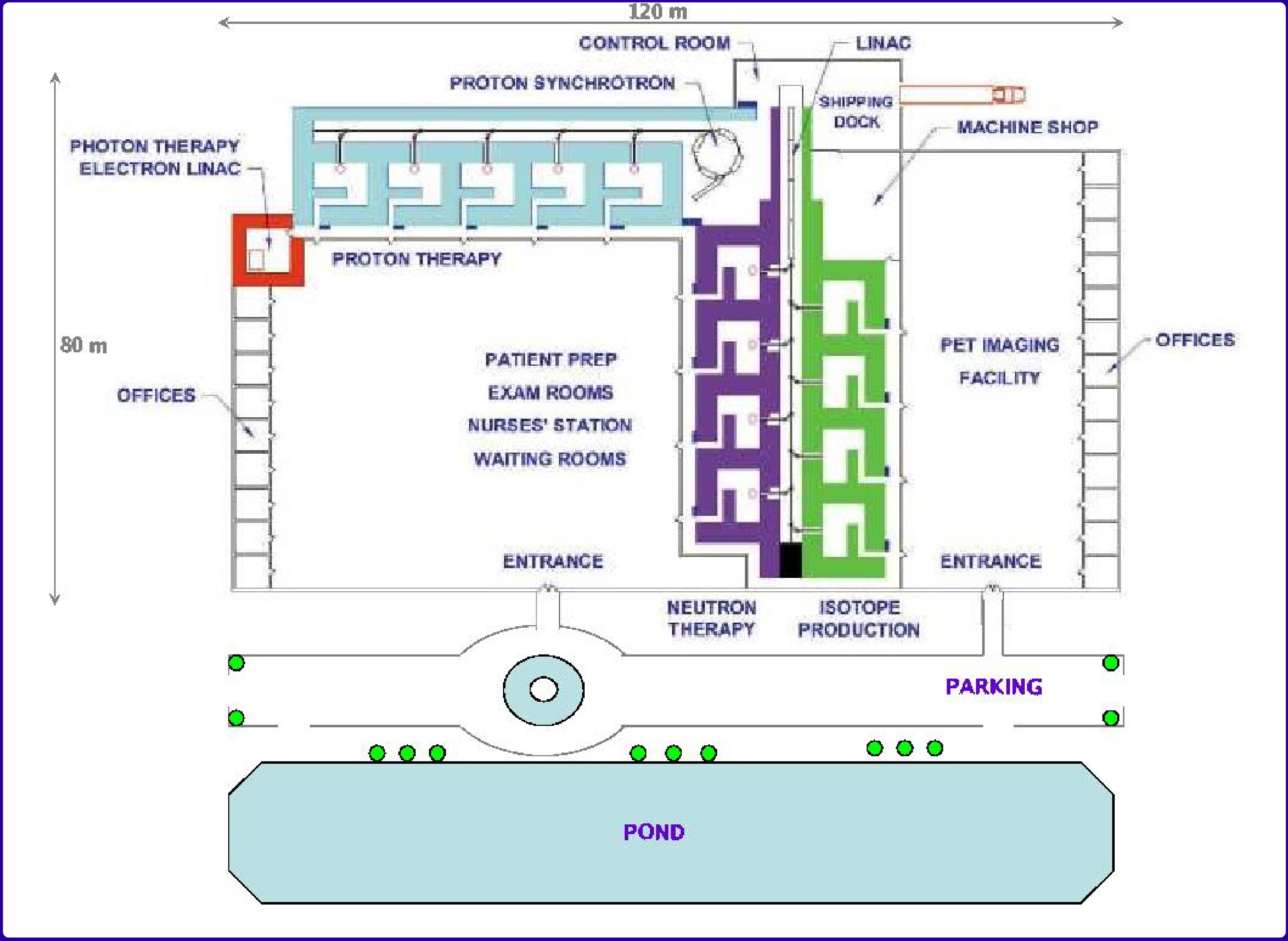
TOTAL of **hadron therapy** every 10 M

about 3'000 pts/year

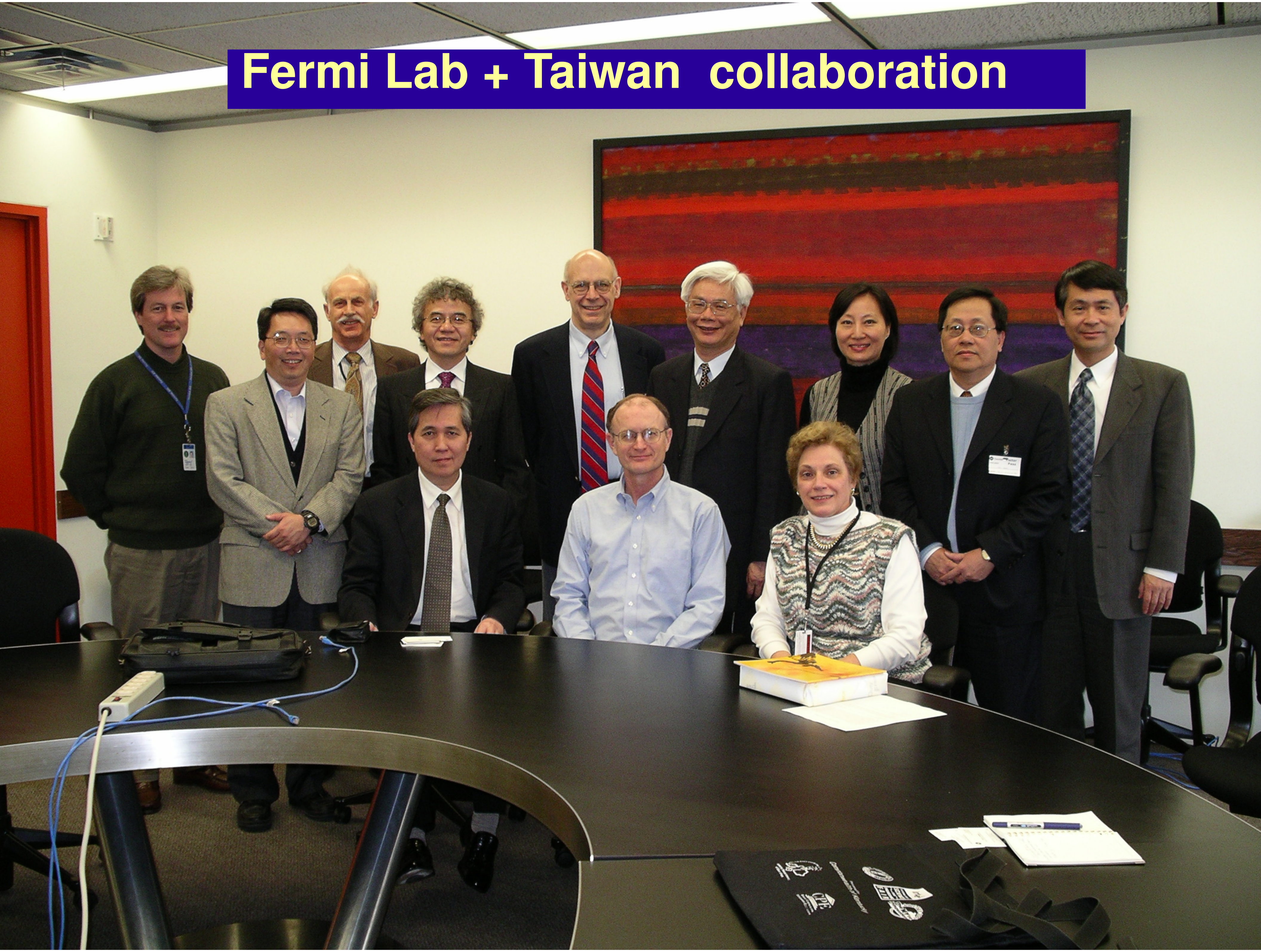
Hadron Therapy is an Important Option for Radiation Therapy Patients.

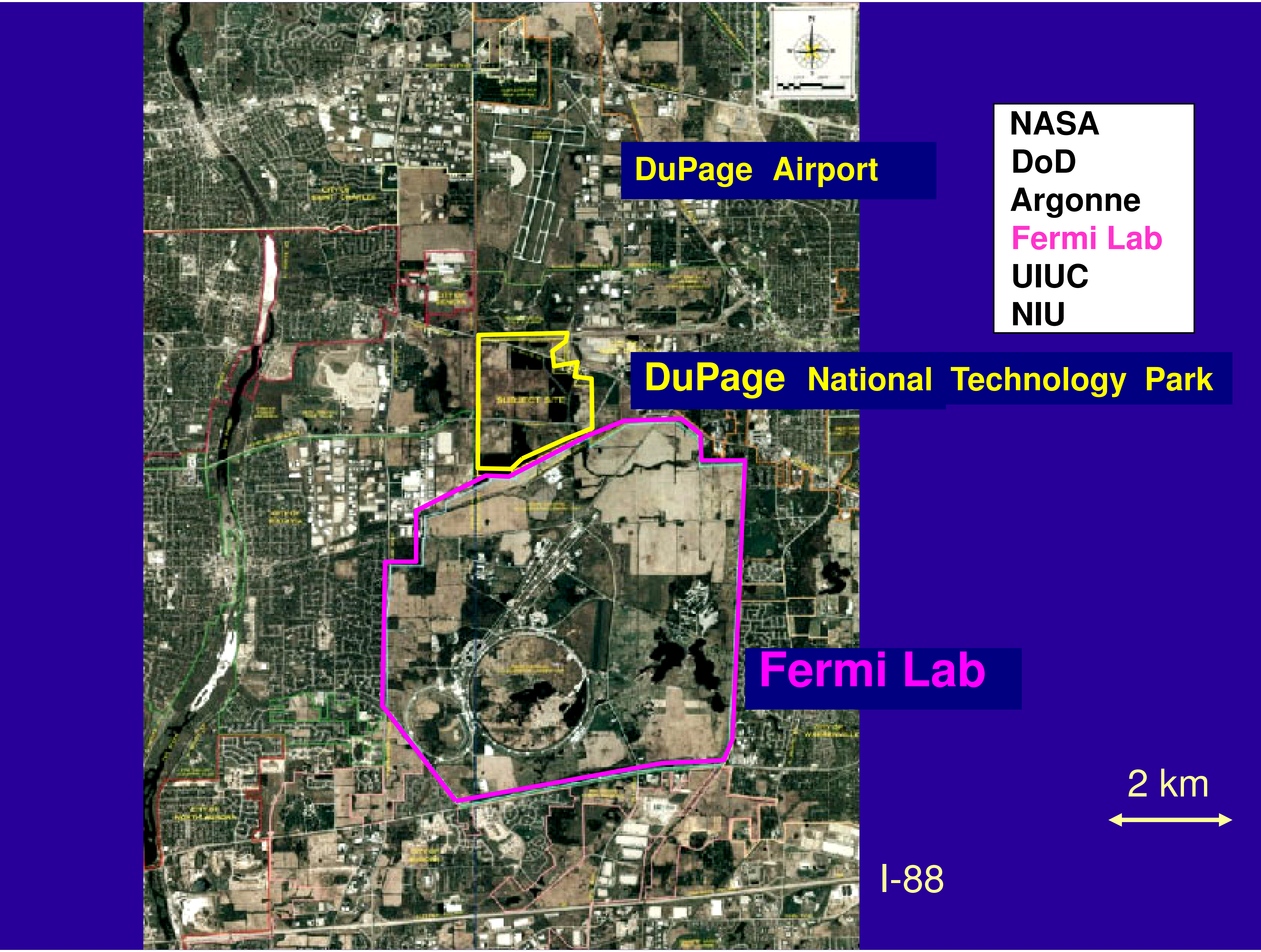


Institute for Hadron Therapy in Illinois & Taiwan



Fermi Lab + Taiwan collaboration




DuPage Airport
NASA
DoD
Argonne
Fermi Lab
UIUC
NIU
DuPage National Technology Park
Fermi Lab
2 km
I-88

Fermi Lab Neutron Therapy

2 Proton Therapy Centers nearby

www.chicagotribune.com/features/lifestyle/health/chi-proton-therapy-bd21-sep21,0,2878089.story

chicagotribune.com

State's bold technology bet

By Jeremy Manier Tribune reporter

September 21, 2008

Proton therapy may be the next big thing in cancer treatment and a wonder of applied physics, but not everyone is convinced that the Chicago area needs two of the expensive, cutting-edge facilities.

State regulators last week approved a $140 million proton therapy center for west suburban Warrenville, to be built just 9 miles from a $159 million device under development in West Chicago. That's a bold bet on the technology, considering that the U.S. as a whole currently has only five proton treatment centers.

What is proton therapy, and why do some doctors think it can improve care for certain kinds of cancer patients? The answer begins with a 1946 paper written by physicist Robert Wilson, who later became Fermilab's first director.

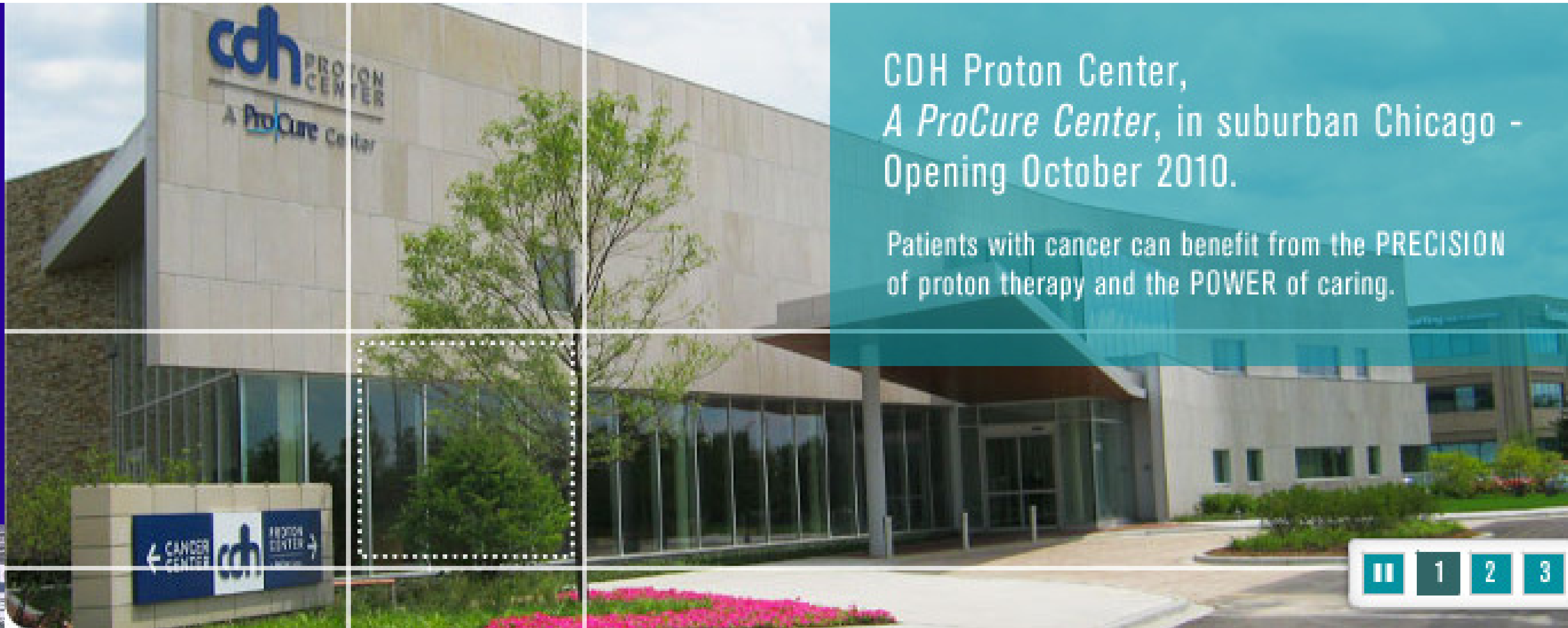
The physics

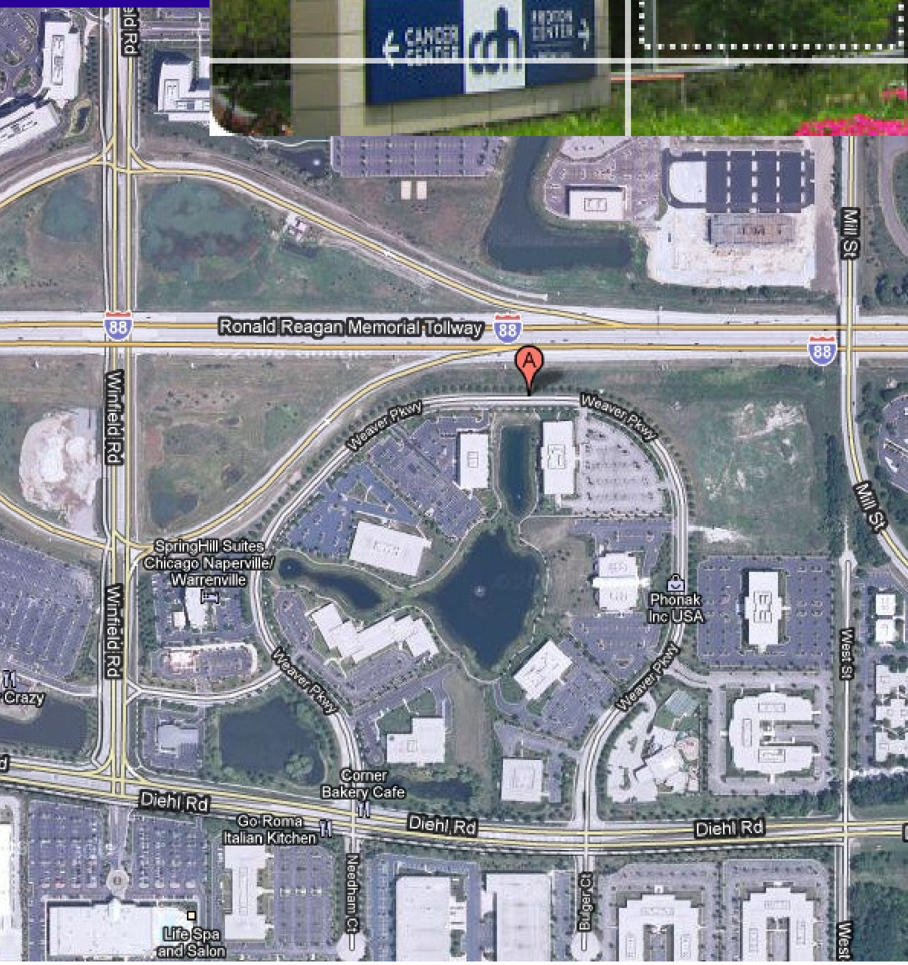
Wilson identified a potentially useful feature of protons, particles that normally are packed tight in the center of atoms. When a beam of protons strikes an object, the particles slow down and then release most of their energy in a quick burst just before they stop entirely.

Wilson realized that the localized burst of energy meant doctors could use protons to precisely target radiation treatment for cancer patients. Like other types of radiation treatment, proton therapy kills cancer cells by destroying their DNA. But other kinds of radiation therapy, such as high-energy X-rays, typically inflict damage on tissue around the tumor.

Proton therapy "minimizes damage to normal good cells in front of the tumor, and delivers no radiation beyond the tumor," said G.P. Yeh, a physicist at Fermi National Accelerator Laboratory, near Batavia, who has worked on such applications.

Fermilab constructed the first hospital-based proton therapy center at Loma Linda University Medical Center in California. In essence such facilities are small versions of Fermilab's mighty particle accelerator.





Central

DuPage

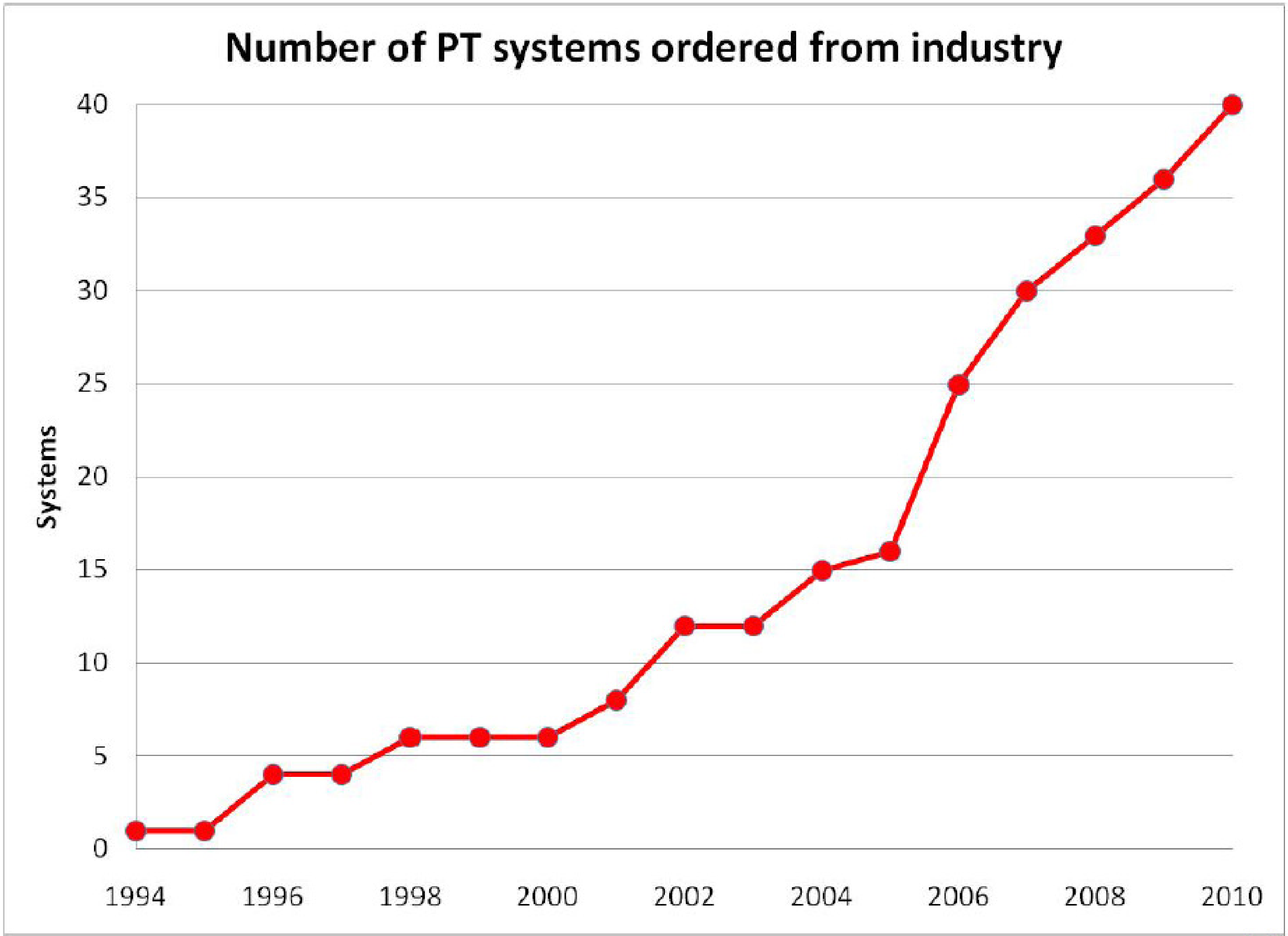
Hospital

Proton Center

IBA 230 MeV resistive isochronous cyclotron

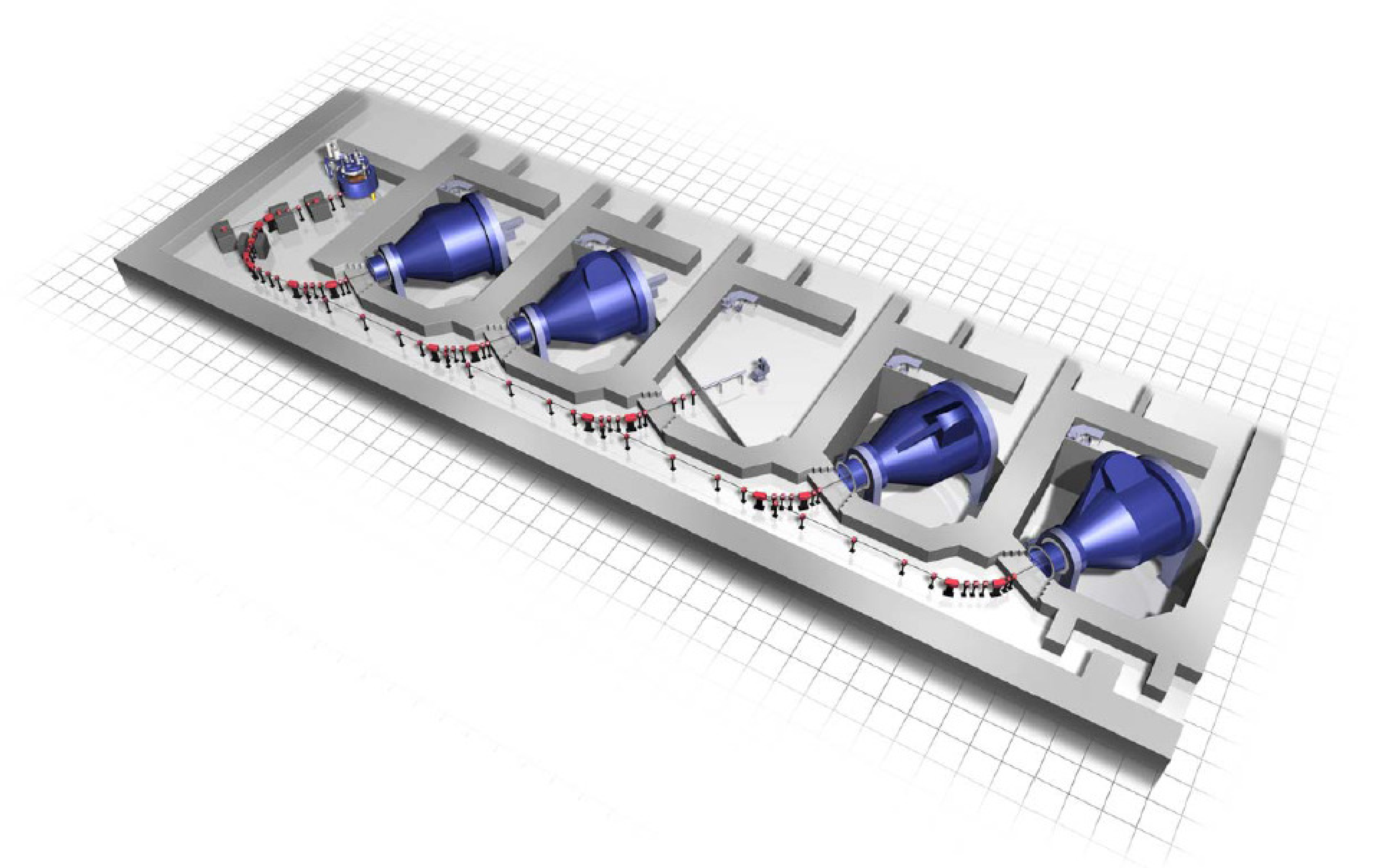
Isocentric gantry treatment room

Number of systems contracted to industry



After NCC, SHI sold one system to Taiwan

ACCEL-Varian PT facility in Munich



Heidelberg ion gantry: patient room

Patient Gantry Room November 2007

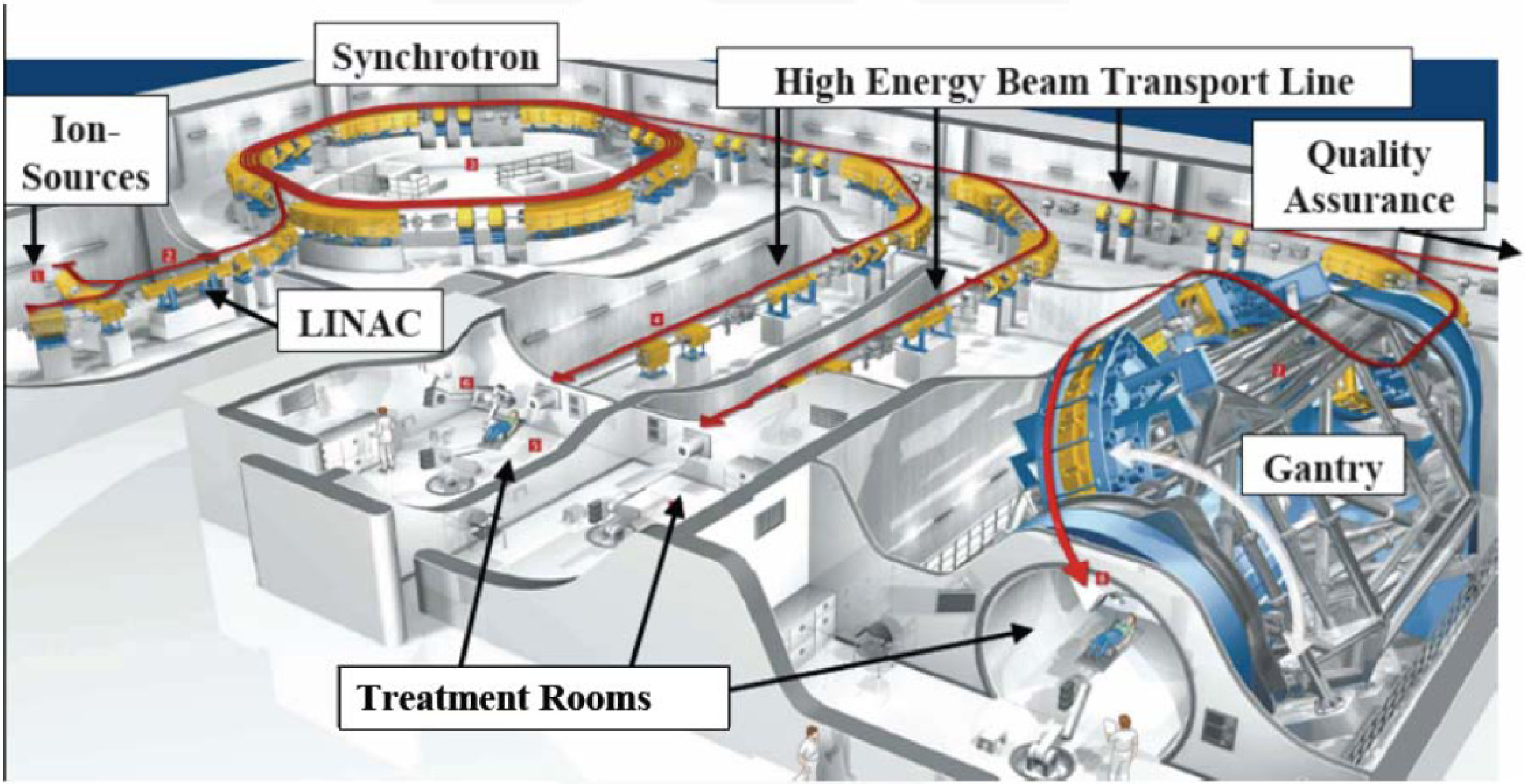
Tilt floor, pending on Gantry position

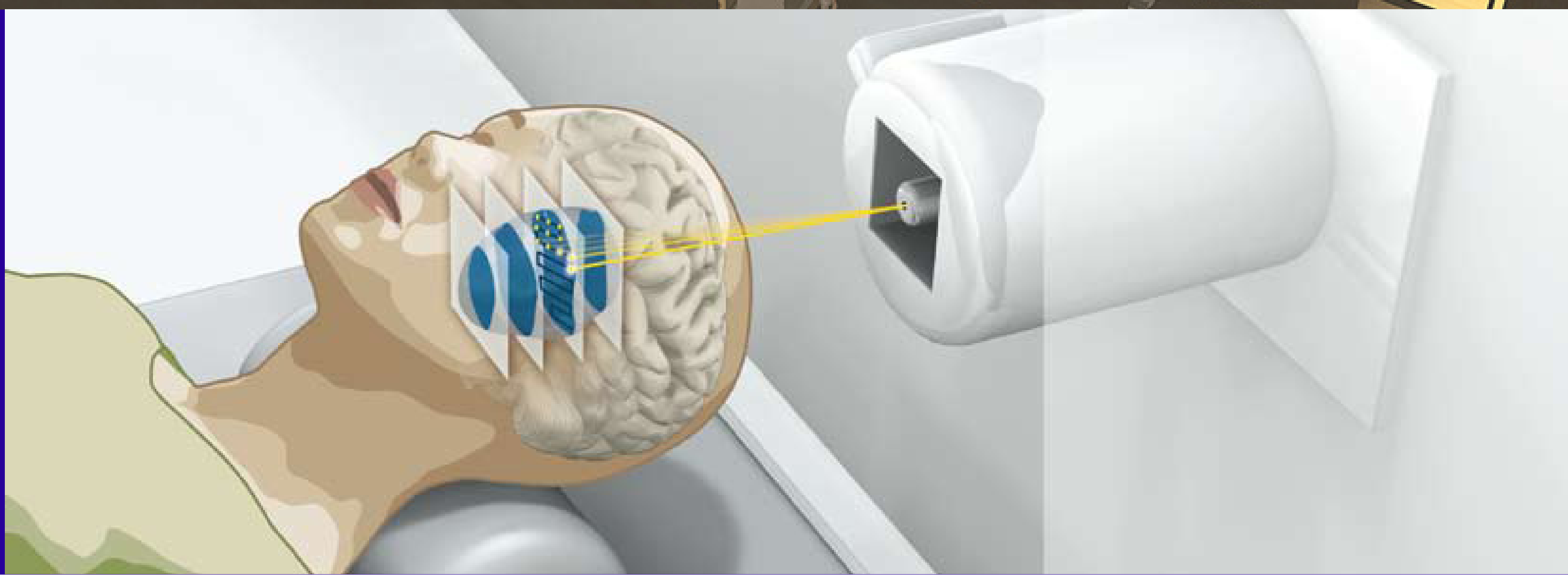
Nozzle

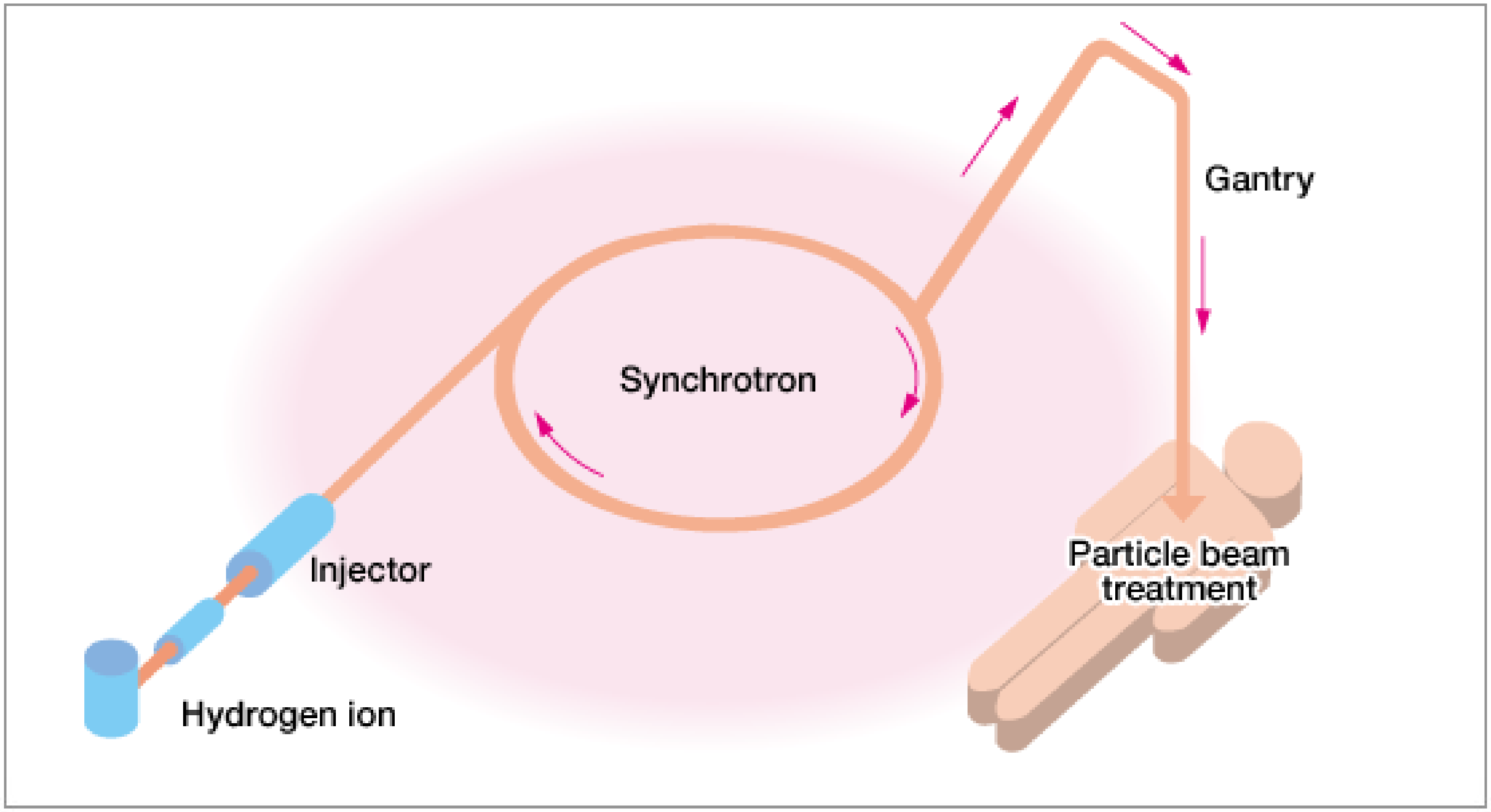
Bumber mats

Patienttable, Roboter

HIT: Heidelberg Ion Therapy Facility

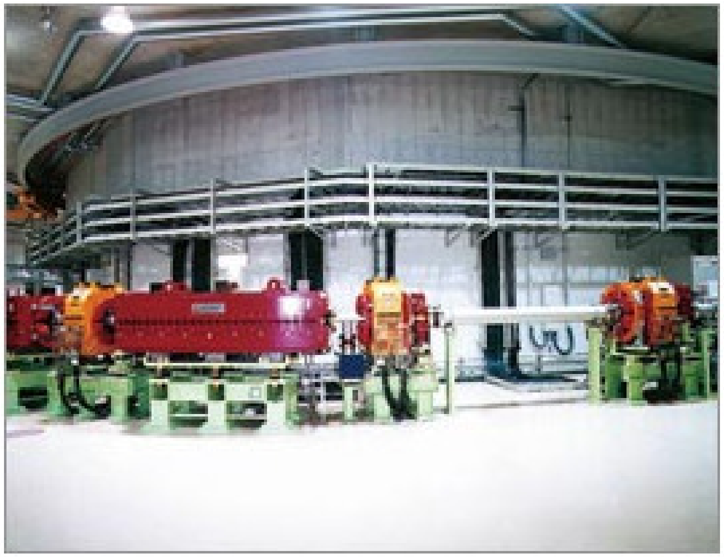




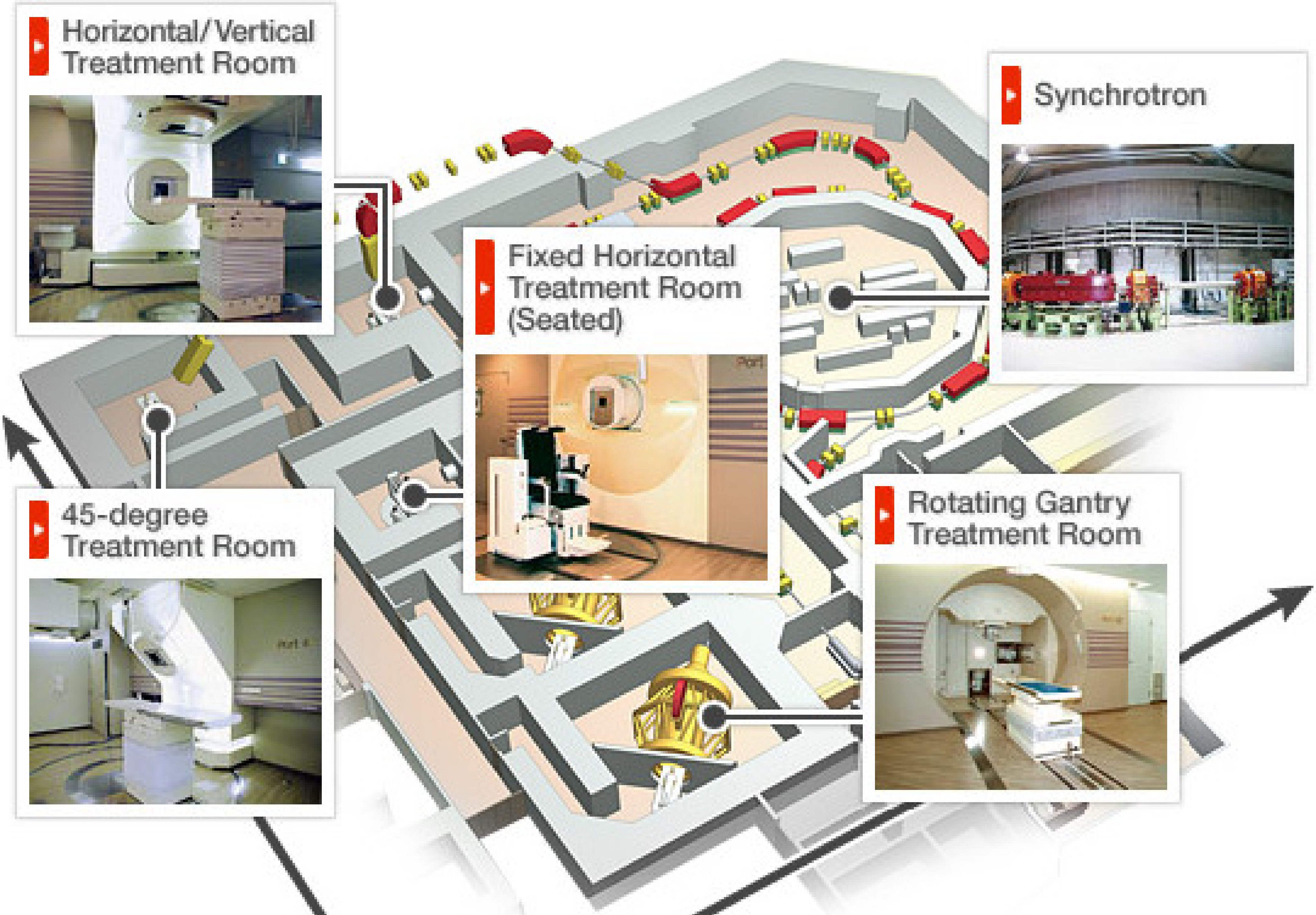


Basic concept for particle beam treatment system

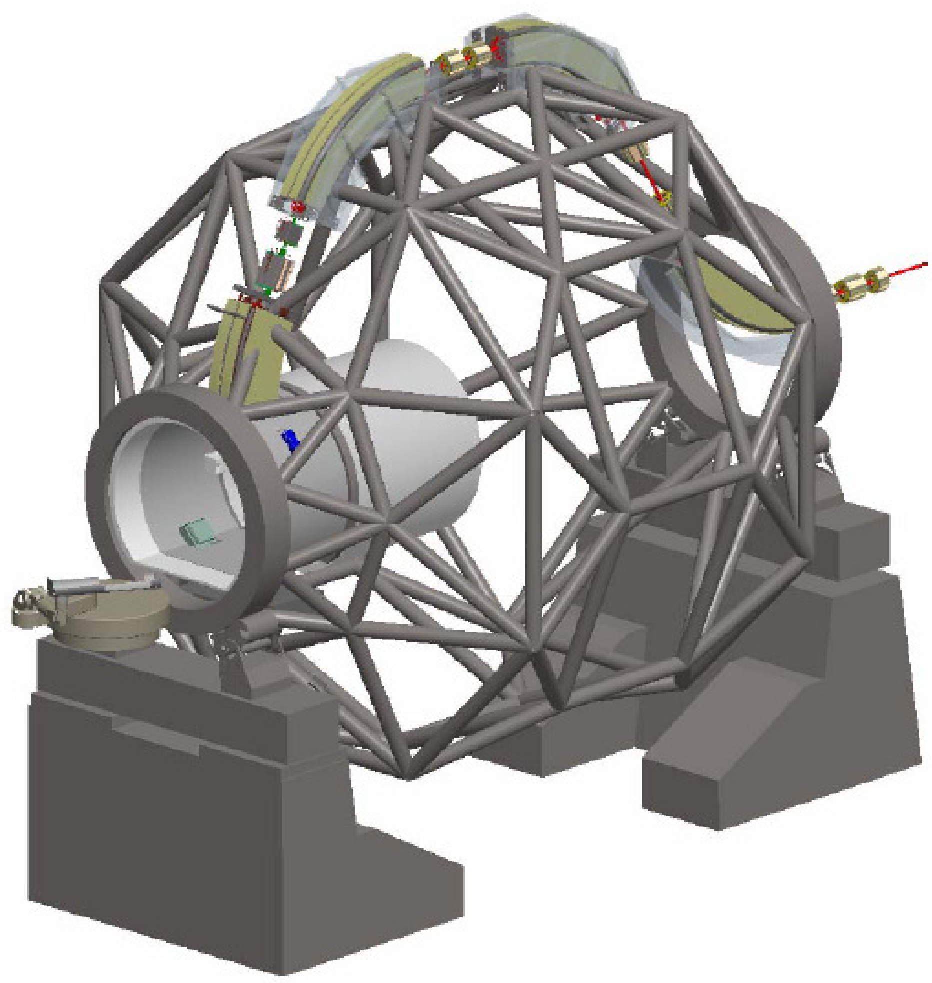
Synchrotron for proton beam



Synchrotron for carbon and proton beam



Horizontal/Vertical Treatment Room
Synchrotron
Fixed Horizontal Treatment Room (Seated)
45-degree Treatment Room
Rotating Gantry Treatment Room



1) IMIT
2) Reduction of Patient's Load

• 3D scanning irradiation	
• Max field size	150 mm^2
• Max SOBP	150 mm
• Max energy	430 MeV/u
• Moving target	OK
• beam size	3~6 mm (1 σ)
• Ene. change	RSF
• Total weight	350 ton

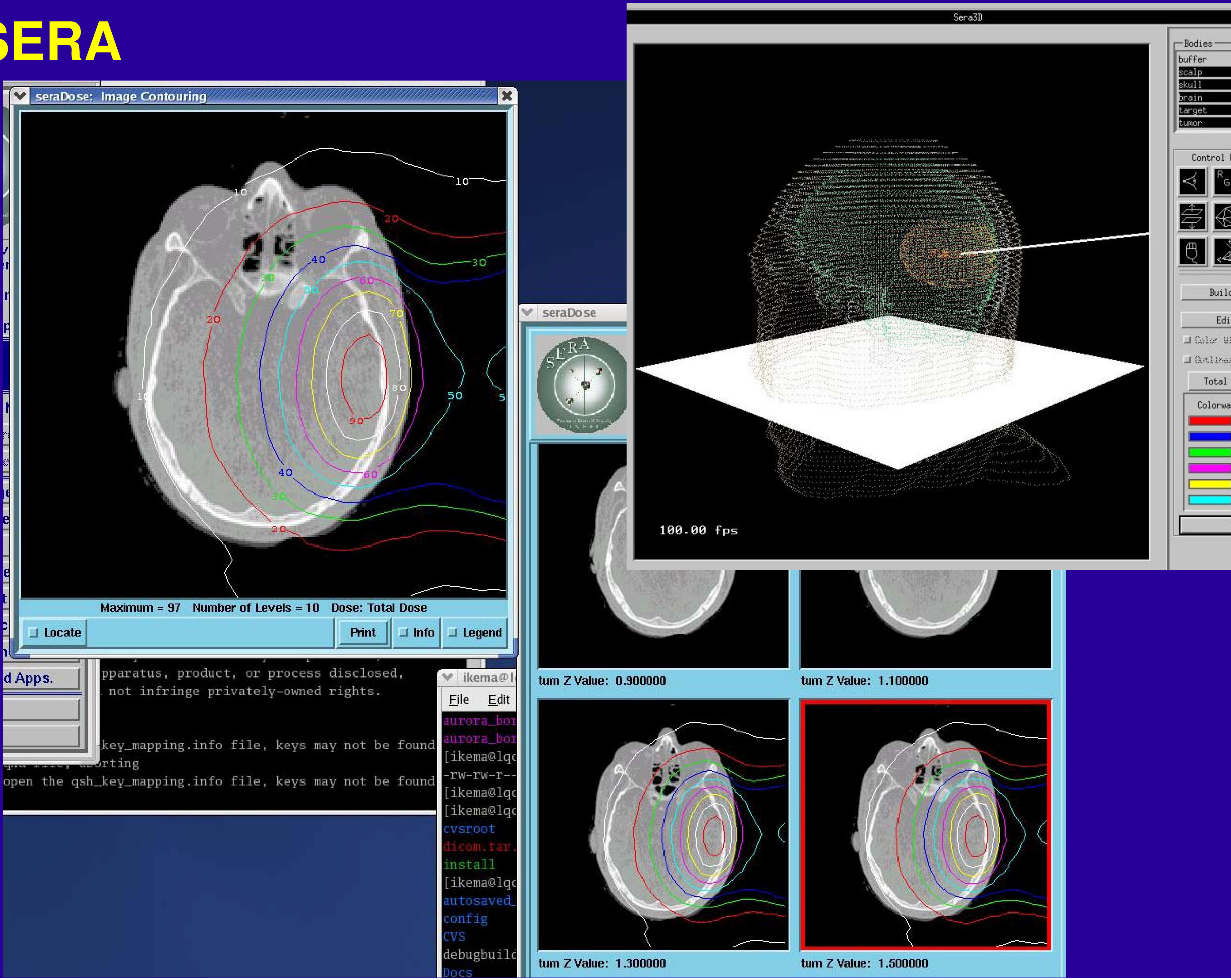
3 new Hadron Therapy Centers in Taiwan

- Chang-Geng Hospital Proton
- T. Guo – NTUH Proton
- Evergreen – EvaAir Carbon / Heavy Ion

Japan & Taiwan

best Healthcare in Asia

SERA



seraDose: Image Contouring
Maximum = 97 Number of Levels = 10 Dose: Total Dose
Locate
Print
Info
Legend
seraDose
Sera3D
Bodies
buffer
scalp
skull
brain
target
tumor
Control Pa
Build
Edit
Total D
Colorwash
100.00 fps
tum Z Value: 0.900000
tum Z Value: 1.100000
tum Z Value: 1.300000
tum Z Value: 1.500000

Hadron Therapy

- Proton Therapy, Heavy Ion Therapy:

  high precision dosage delivery to tumors

  minimize damage to normal cells

- Neutron Therapy, Heavy Ion Therapy:

  high Relative Biological Effectiveness

- New Hadron Therapy Centers worldwide

  3 in Taiwan, 2 in Illinois

Excellent treatment for fighting cancer