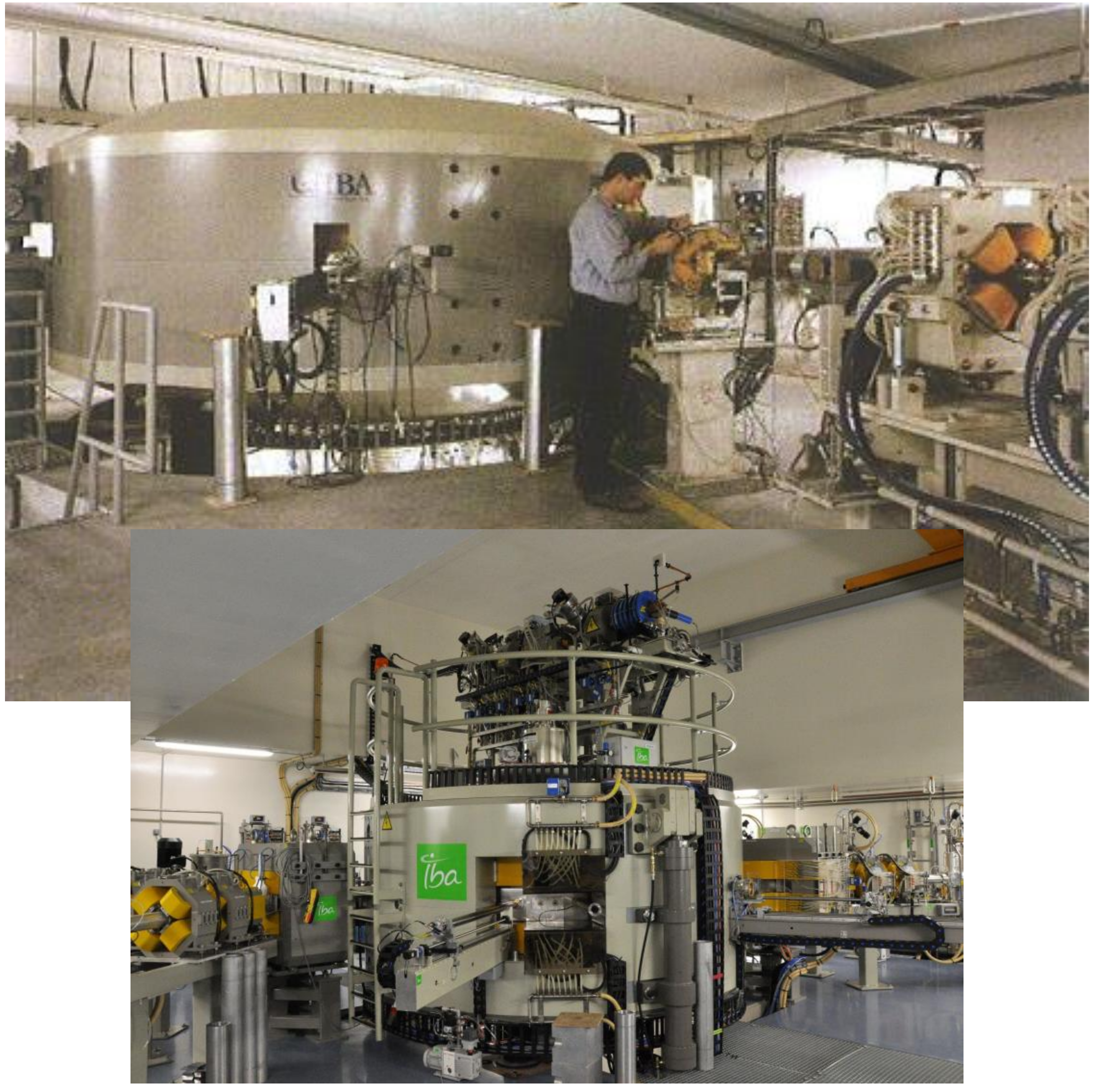
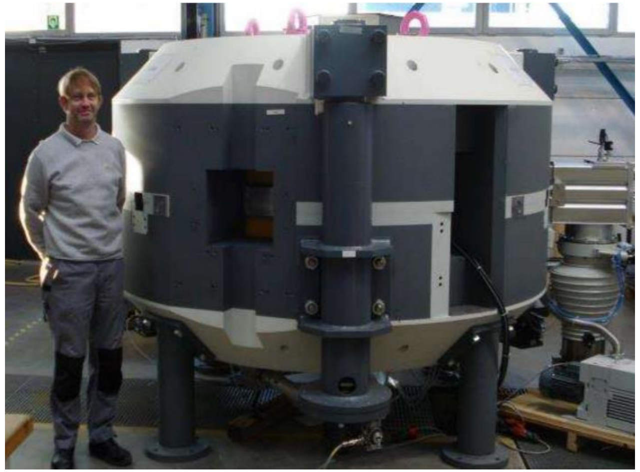
Accelerators at IBA

June 2019


Future
Circular
Collider
Geneva
PS
SPS
LHC
100 km
27 km

An alternative offer?





Many others available…!

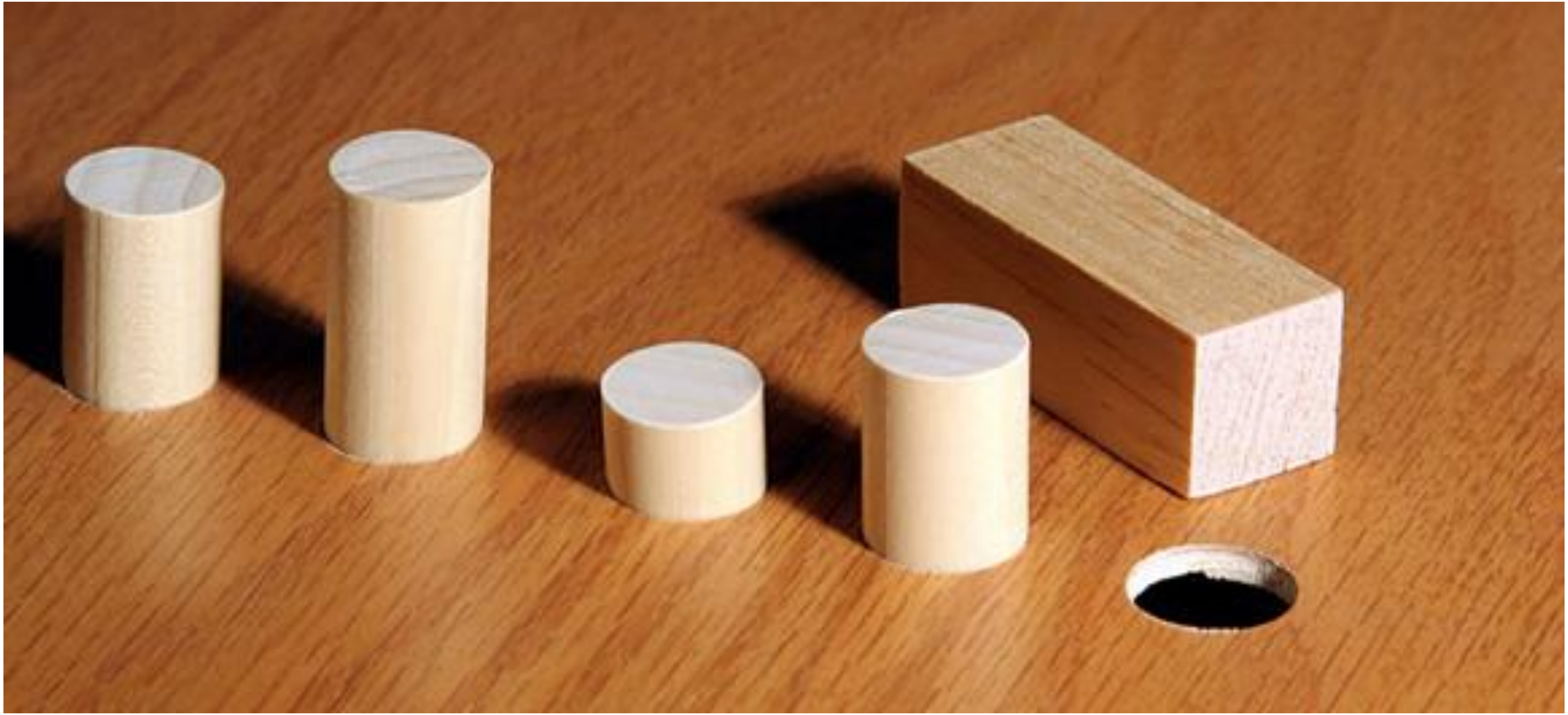
An alternative offer?

	HL-LHC	FCC-hh	Kiube	Cyclone 70	Cyclone 230	S2C2
Beam energy (TeV)	7	50	1,80E-05	7,00E-05	2,30E-04	2,30E-04
circumference (km)	26,7	100	6,00E-03	1,20E-02	1,40E-02	8,00E-03
Dipole field (T)	8,33	16	1,3	1,1	3	5,7
Injection energy (TeV)	0,45	3,3	1,00E-08	4,00E-08	1,00E-08	1,00E-08
Transverse normalized emittance (µm)	2,5	2,2	~1,2	~8,7	~18	~60
beam current (A)	1,12	0,5	3,00E-04	7,50E-04	5,00E-07	1,50E-07
RMS IP spot size (µm)	7,1	6,8	1,00E+04	1,00E+04	3,00E+03	3,00E+03

	LEP2	FCC-ee	TT50	TT1000	TT300HE
Beam energy (GeV)	104	175	1,00E-02	8,00E-03	4,00E-02
circumference (km)	26,7	100	5,60E-03	1,00E-02	9,00E-03
H-V transverse normalized emittance (pm)		1,3-0,0025	1,93E+05		2,58E+05
beam current (mA)	3,04	6,6	2	100	3
H-V RMS IP spot size (µm)	182-3,2	36-0,07	5000-10000	5000-10000	5000-10000

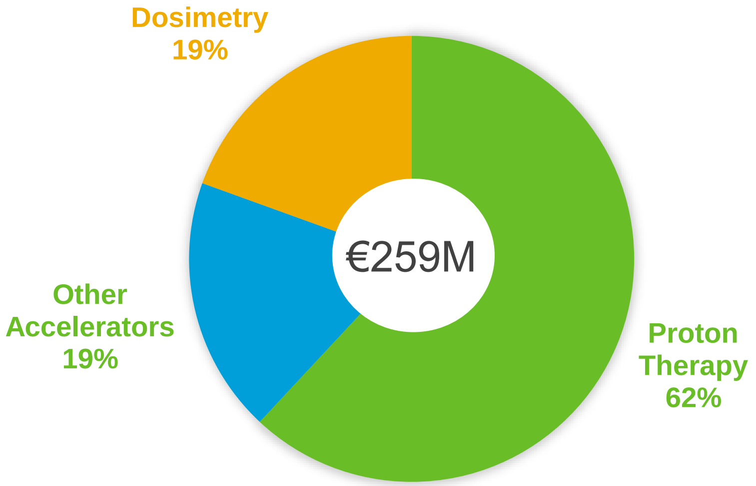
So… What do you think?

So… What do you think?



IBA today

- A world leading innovator in cancer diagnostics and treatment
  - Number one provider of proton therapy solutions
  - Global leader in RadioPharma and Industrial Solutions
- 1,400 employees worldwide
- Most advanced PT offering
  - Single and multi room systems equipped with cutting edge technology



December 2018
With IBA dosimetry

*Proteus®ONE and Proteus®PLUS are brand names of Proteus 235

Outline

What we do and a few interesting things from our applications

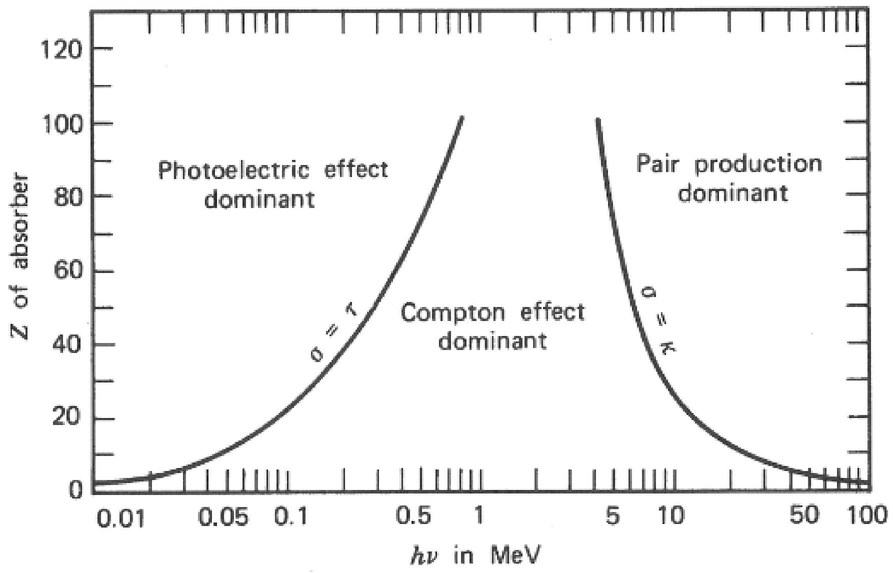
- Protontherapy Systems and some highlights
- Radiopharmaceutical Solutions and Theranostics
- Industrial Applications and system Flexibility
- Final thoughts

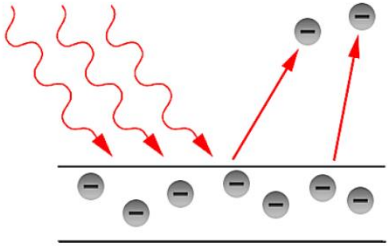
	HL-LHC	FCC-hh	Kiube	Cyclone 70	Cyclone 230	S2C2
Beam energy (TeV)	7	50	1,80E-05	7,00E-05	2,30E-04	2,30E-04
circumference (km)	26,7	100	6,00E-03	1,20E-02	1,40E-02	8,00E-03
Dipole field (T)	8,33	16	1,3	1,1	3	5,7
Injection energy (TeV)	0,45	3,3	1,00E-08	4,00E-08	1,00E-08	1,00E-08
Transverse normalized emittance (µm)	2,5	2,2	~1,2	~8,7	~18	~60
beam current (A)	1,12	0,5	3,00E-04	7,50E-04	5,00E-07	1,50E-07
RMS IP spot size (µm)	7,1	6,8	2000	2000	3000	3000

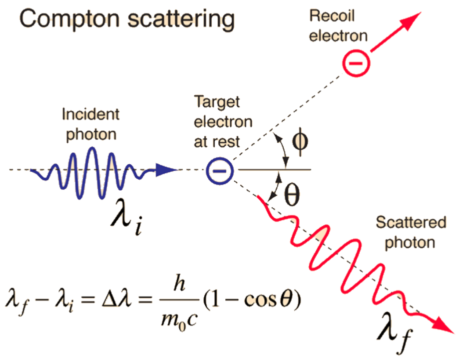
Proton Therapy

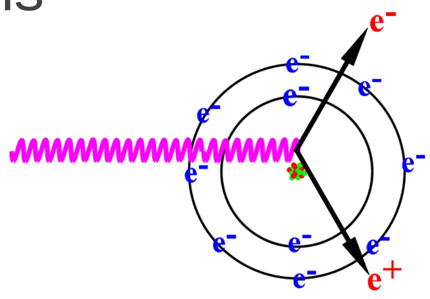
« Conventional » Radiation Therapy vs. Hadrontherapy

- Most conventional radiation therapy and arc therapy systems use xrays of a few MeV for cancer treatment
  - Dose is not delivered to tissues by the photons themselves, but rather through secondary electrons produced by 3 mechanisms









G.F. Knoll – Radiation detection and measurement, Wiley

« Conventional » Radiation Therapy vs. Hadrontherapy

- Results in:
  - A decrease of photon numbers following a superimposition of decreasing exponentials
  - electron buildup

=> dose builds-up and then ~exponentially decreases with depth once electron equilibrium is reached

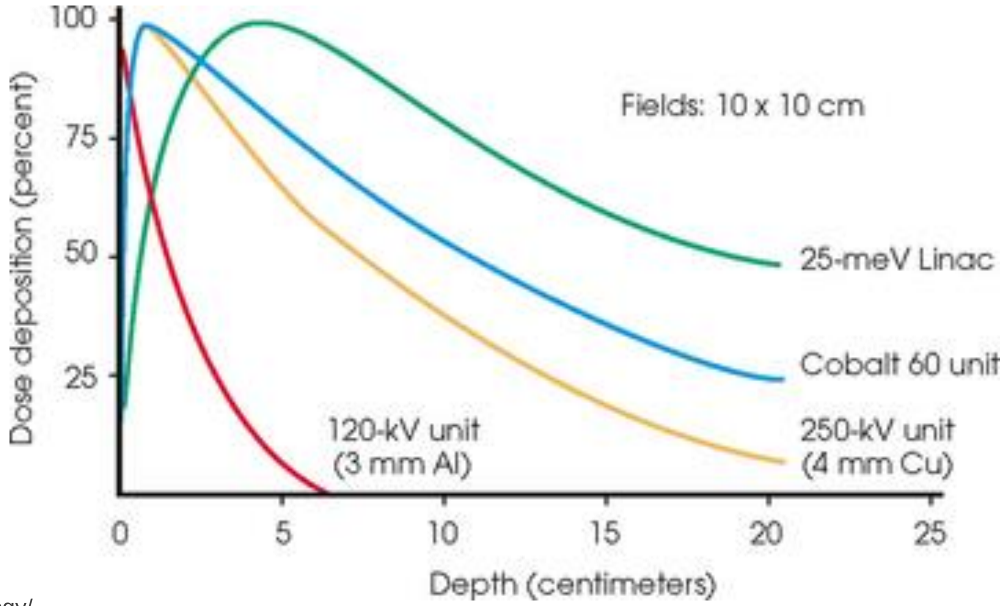


Image courtesy of http://radiologykey.com/radiation-oncology/

« Conventional » Radiation Therapy vs. Hadrontherapy

- Instead, hadrons lose their energy in matter according to Bethe-Bloch formula:

$$-\frac{dE}{dx} = 2\pi N_A {r_e}^2 m_e c^2 \rho \frac{Z}{A}\frac{z^2}{\beta^2}\left[\ln\left(\frac{2m_e\gamma^2 v^2 W_{max}}{I^2}\right) - 2\beta^2 - \delta^2 - 2\frac{C}{Z}\right]$$

Shell correction

Density correction

Where

$$W_{max} = \frac{2m_e c^2\beta^2\gamma^2}{1+2\frac{m_e}{M}\sqrt{1+\left(\frac{m_e}{M}\right)^2+\beta^2\gamma^2}} \approx 2m_e c^2\beta^2\gamma^2$$ is head-on collision energy transfer

And $I(eV) = Z\left(12+\frac{7}{Z}\right)$ for Z<13

$I(eV) = Z(9.76 + 58.8Z^{-1.19})$ for Z≥13 is the average ionization potential of the absorber

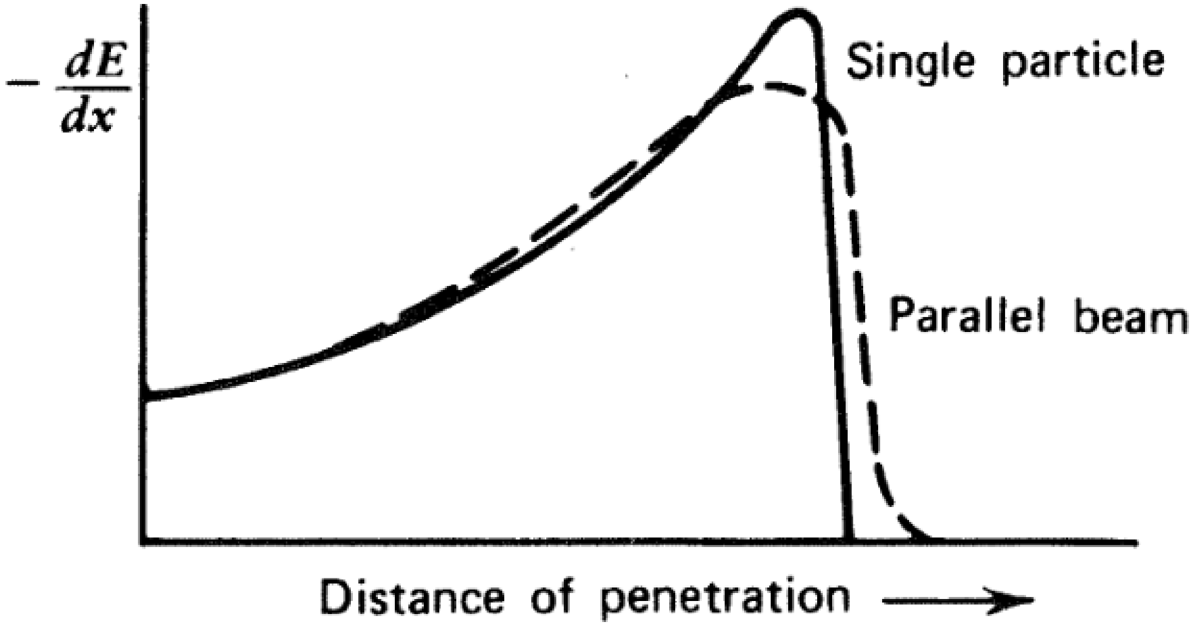
And

$$Z \to Z_{eff} = \sum a_i Z_i$$
$$A \to A_{eff} = \sum a_i A_i$$
$$\ln(I) \to ln(I_{eff}) = \sum \frac{a_i Z_i ln(I_i)}{Z_{eff}}$$
$$\delta \to \delta_{eff} = \sum \frac{a_i Z_i \delta_i}{Z_{eff}}$$
$$C \to C_{eff} = \sum a_i C_i$$

Compound materials

« Conventional » Radiation Therapy vs. Hadrontherapy

- In short, it results in the famous « bragg peak » dose distribution



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.

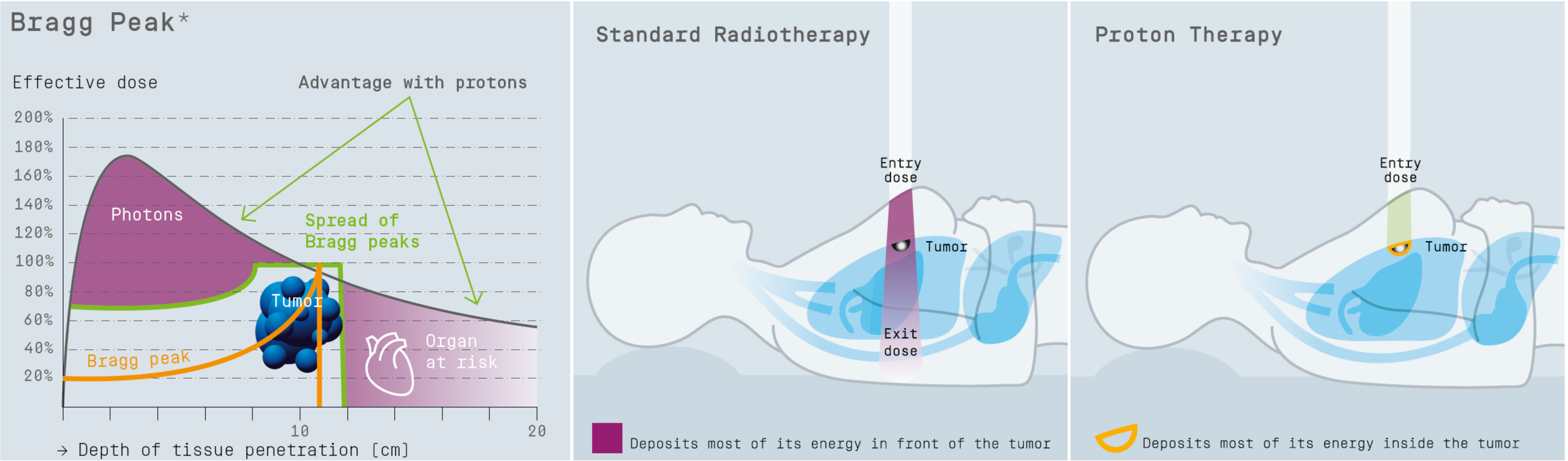
To be as simple as possible, let us consider only high-energy protons: later we can generalize to other particles. The accelerators now being constructed or planned will yield protons of energies above 125 MeV (million electron volts) and perhaps as high as 400 MeV. The range of a 125 MeV proton in tissue 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.

G.F. Knoll – Radiation detection and measurement, Wiley

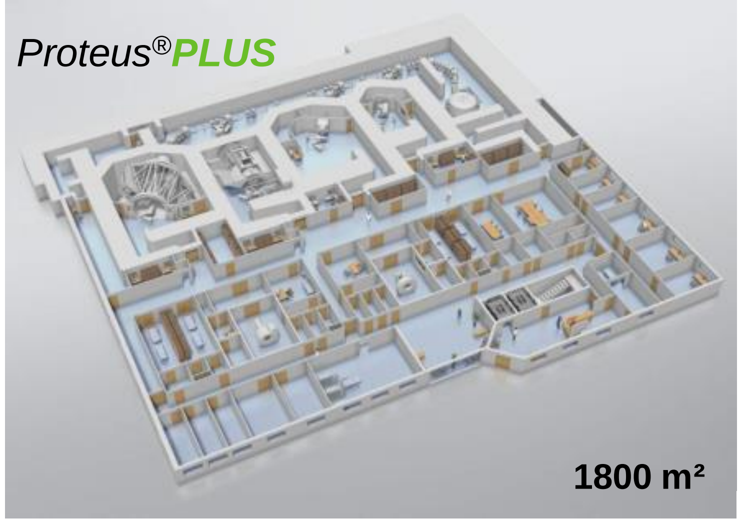
Dose Conformation

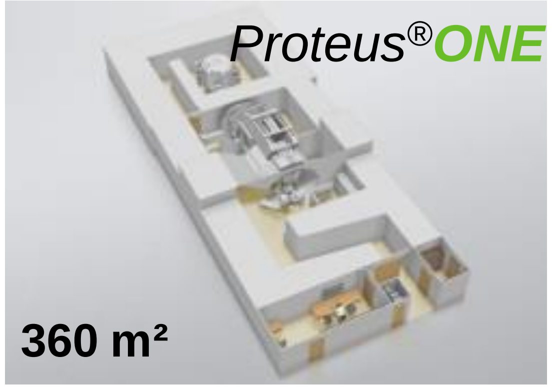
Protons:

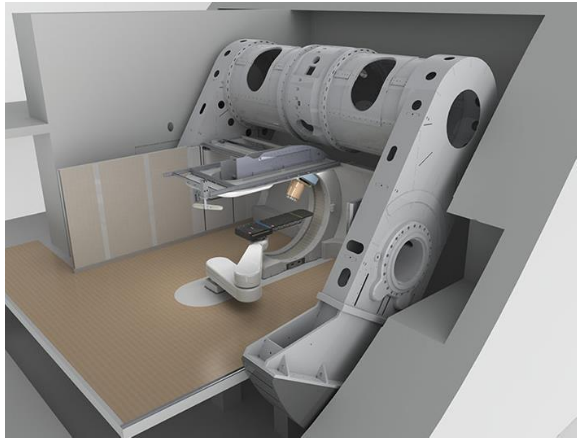
- Minimal radiation exposure of healthy organs
- Potential to reduce the risk of secondary cancers
- Potential to improve the quality of life for patients during and after treatment
- Possibility of retreatment

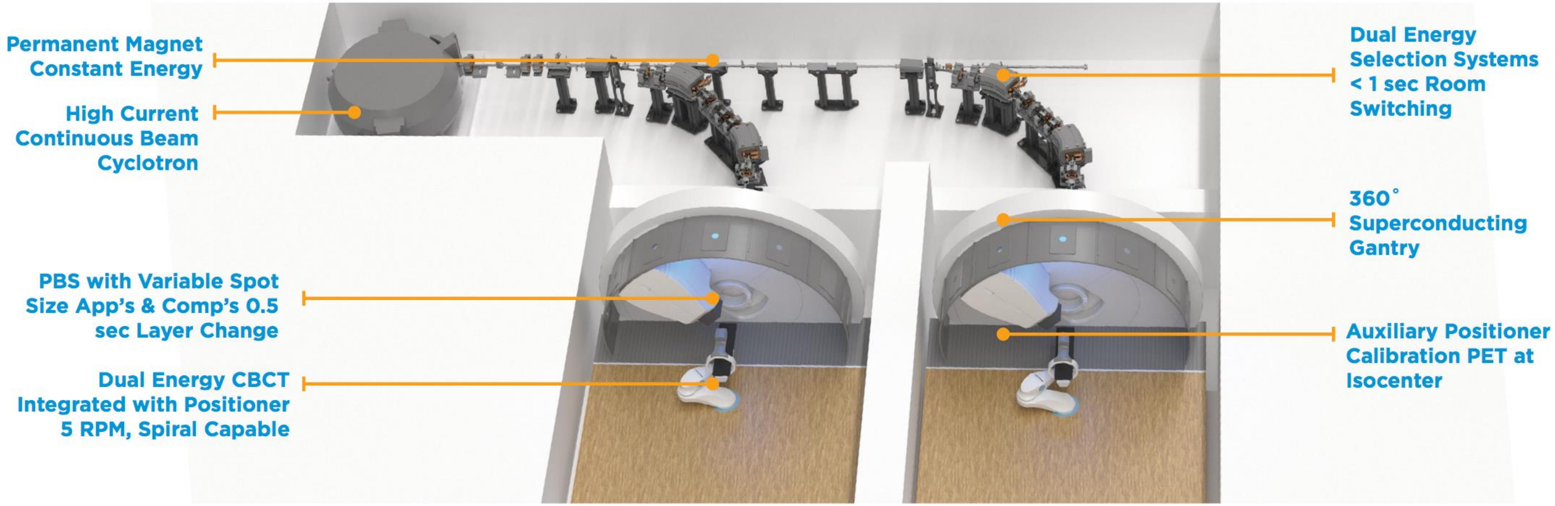


What does a system look like?





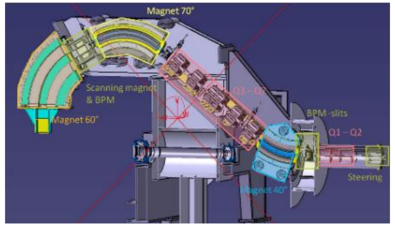


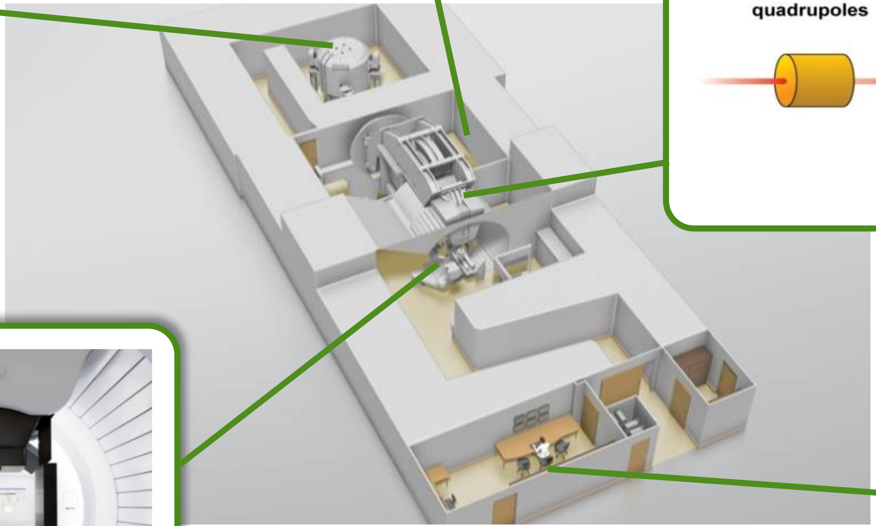


What does a system look like?

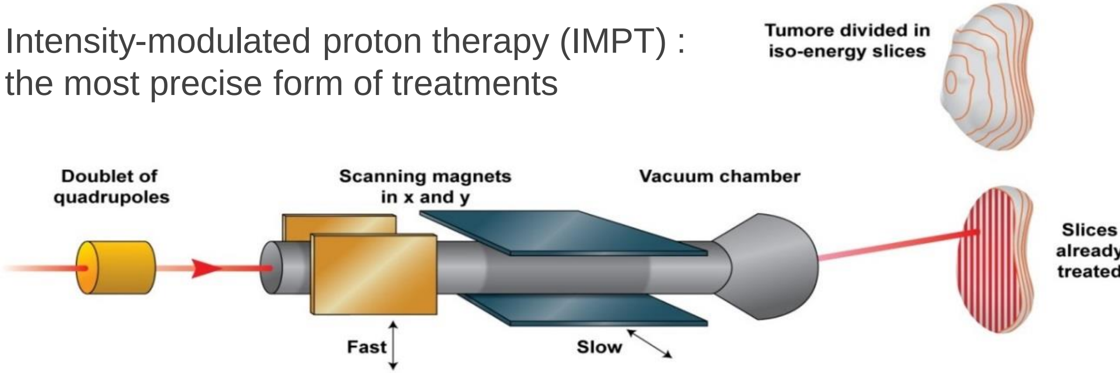
Compact super-conducting accelerator for producing the energetic proton beam

A rotating gantry to set the beam at the right angle





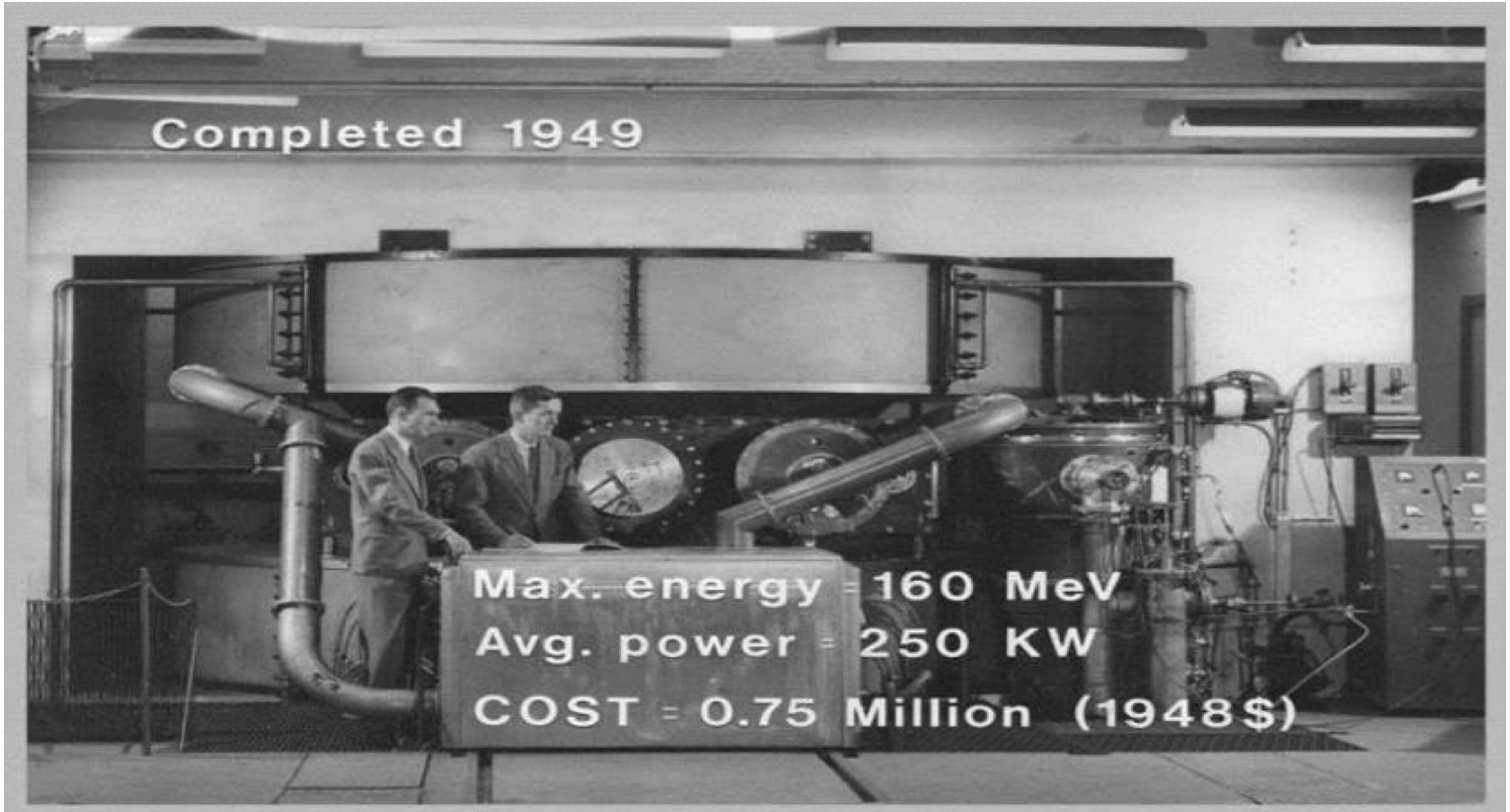
Intensity-modulated proton therapy (IMPT) :
the most precise form of treatments



Stereoscopic imaging and CBCT at isocentre:
accurate patient setup,
quality images for adaptive treatments

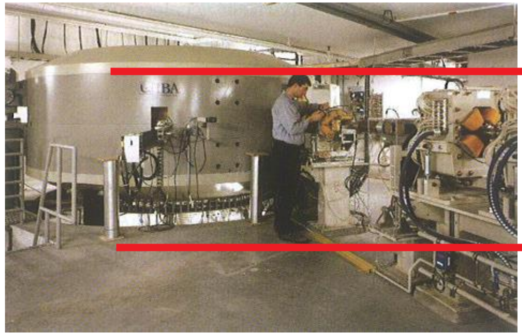
Efficient software integration,
enabling easy & flexible workflows

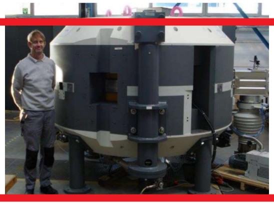
Accelerators – (Synchro-)Cyclotrons



(L) Dr. Lee Davenport (R) Dr. Norman Ramsey
June 10 1949

Accelerators – (Synchro-)Cyclotrons





IBA C230
- 230 MeV protons
- 4.3 m Diameter
- CW beam
- Normal conducting
- Magnet: 200 kW
- RF: 60 kW

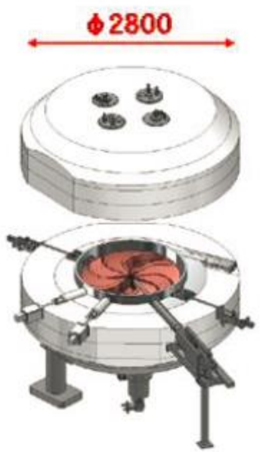
Varian-Accel Probeam
- 250 MeV protons
- 3.1 m Diameter
- CW beam
- Superconducting (NbTi)
- Magnet: 40 kW
- RF: 115 kW

Mevion SC250
- 250 MeV protons
- ~1.5 m Diameter (shield)
- Superconducting (Nb3Sn)

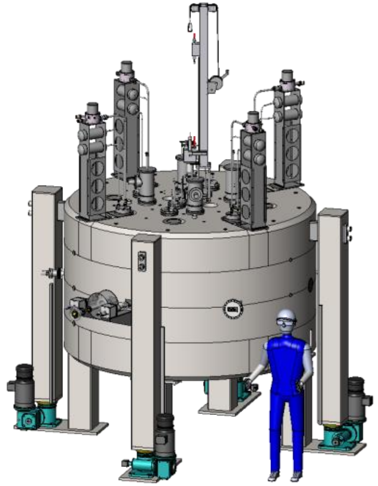
IBA S2C2
- MeV protons
- 2.2 m Diameter
- Rep. rate: 1 kHz
- Superconducting (NbTi)
- RF: 11 kW

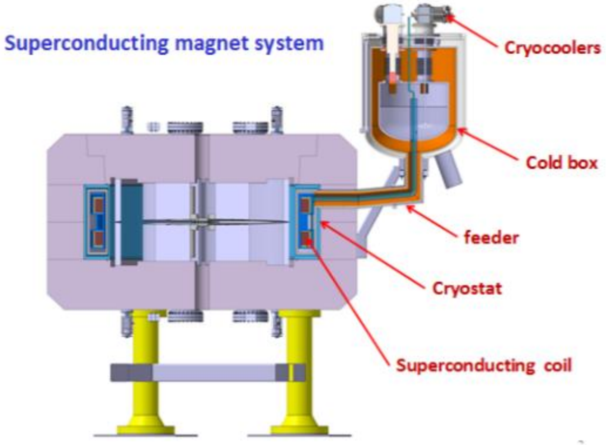
Accelerators - Ongoing developments

- 1. Isochronous: SHI, Varian/Antaya, Pronova/Ionetix, Heifei/JINR

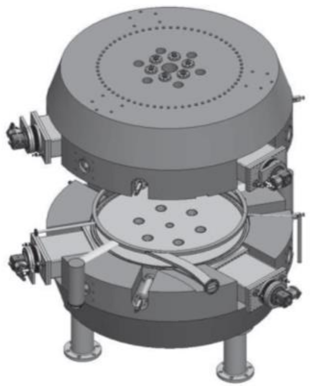


Ant


Derenchuck - NAPAC 2016



Karamysheva - THP20 cyclotrons 2016


Antaya – CAS 2015

SHI
- 230 MeV protons
- 2.8 m Diameter
- CW beam
- Superconducting (NbTi)
- 65 tons
- 4 T (extr.)

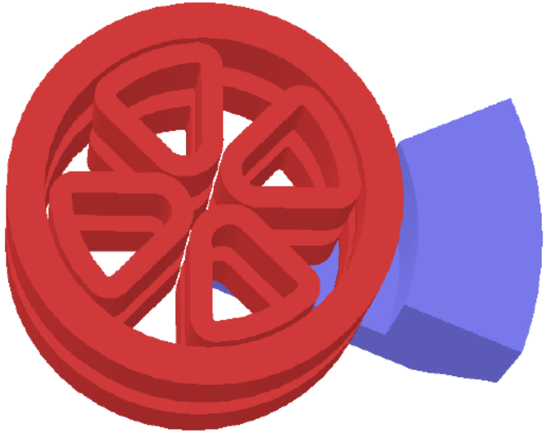
Pronova/Ionetix
- 250 MeV protons
- 2.8 m Diameter
- CW beam
- Superconducting (Nb_3Sn)
- 60 tons
- 3.7 T (extr)

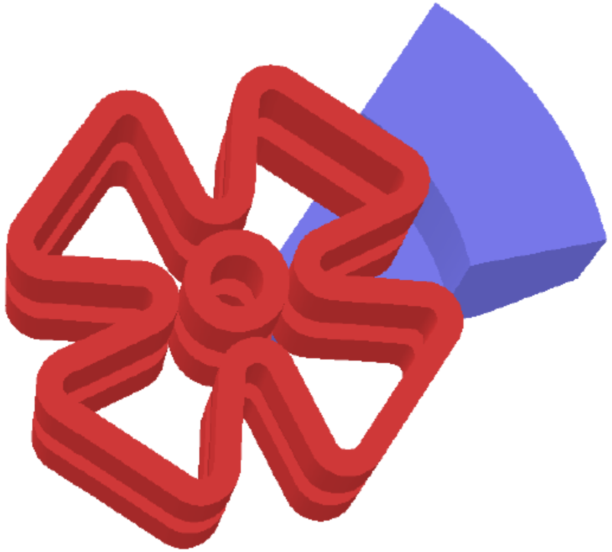
Heifei/JINR
- 200 MeV protons
- 2.2 m Diameter
- CW beam
- Superconducting
- 30 tons
- 3.6 T (extr.)

Varian/Antaya
- 230 MeV protons
- 2.2 m Diameter
- CW beam
- Superconducting (Nb_3Sn)
- 30 tons+
- 5.5 T (extr.)
- “Flutter” coils

Dealing with the Limitations of Iron-Dominated Magnets

- Flutter coils are useful to overcome the limitation of iron-dominated field variation





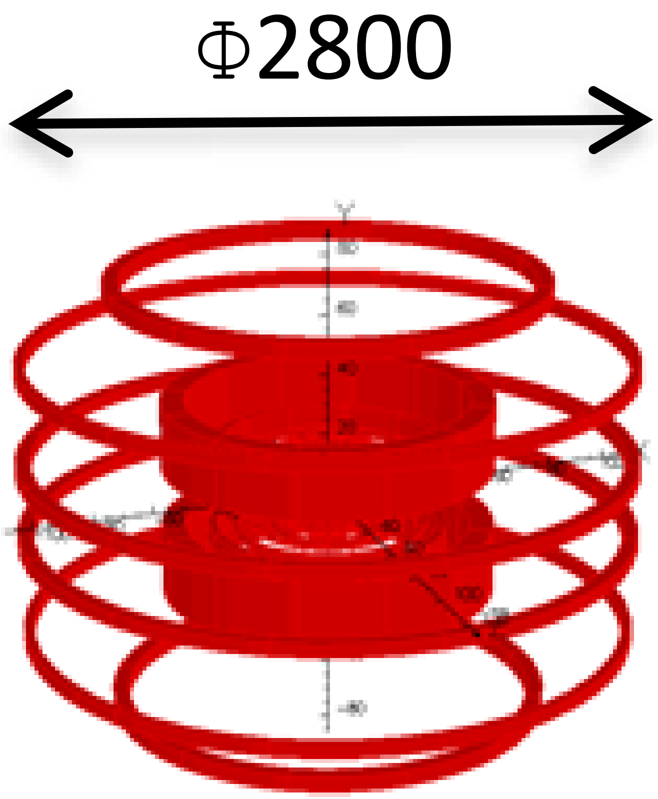
Kleeven, IBA internal report

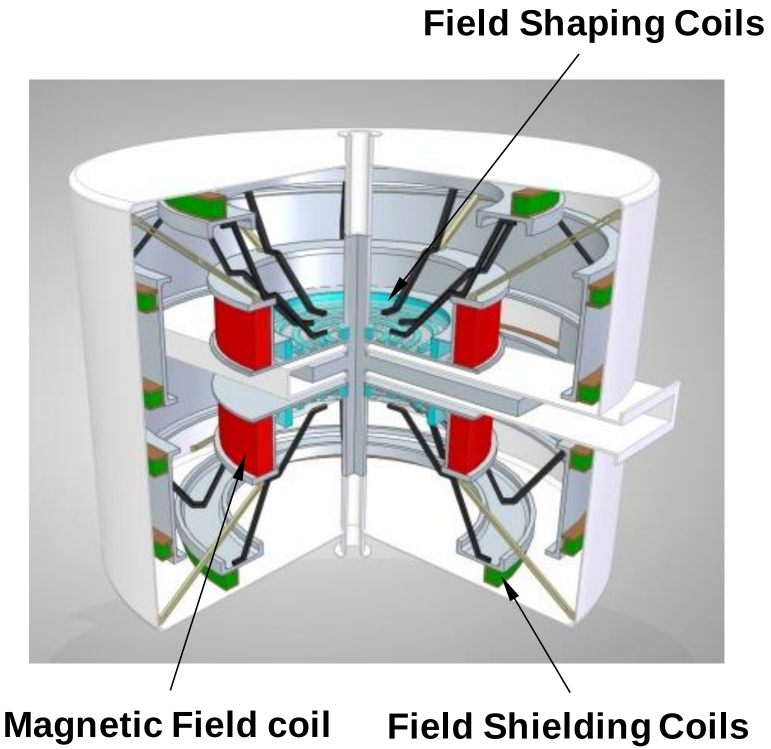
Antaya – Private communication

- Same concept can be used for extraction systems
- Limitations:
  - Adds complexity (cryogenics closer to median plane)
  - Less sharp field variations

Proton cyclotrons - Ongoing developments

- 2. Synchrocyclotrons: MIT ironless (Pronova)

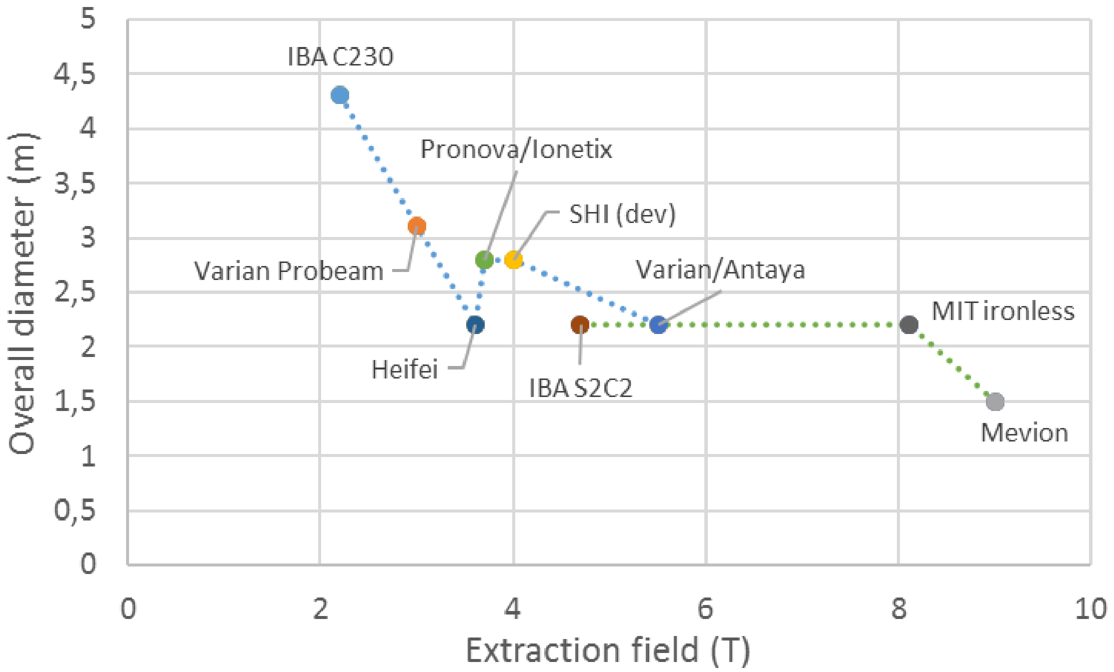


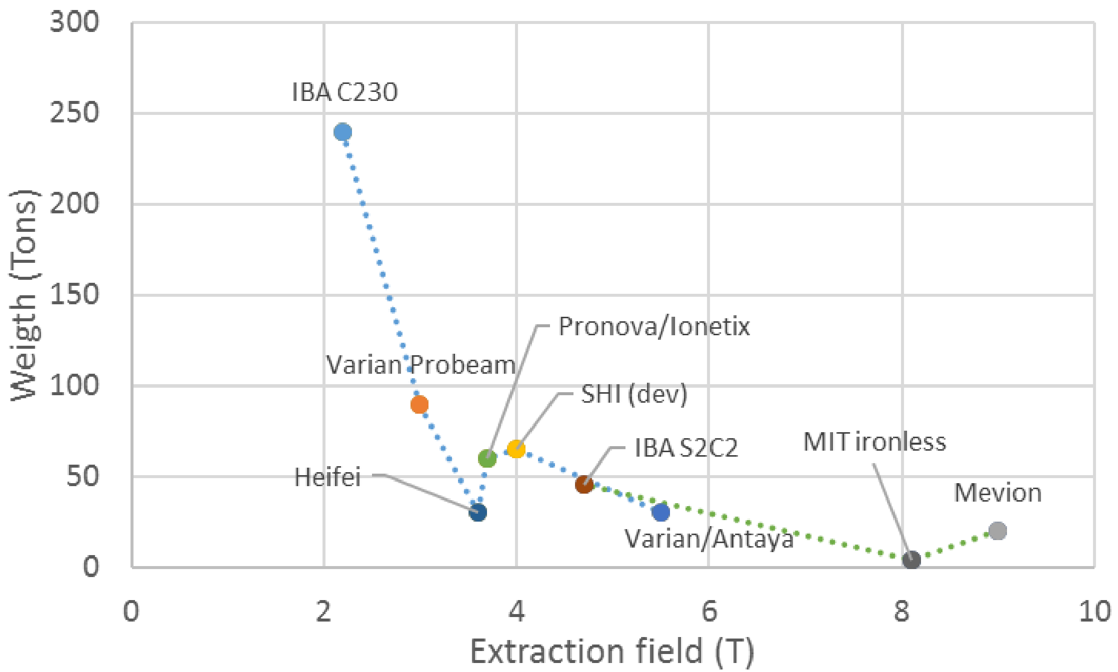


- 250 MeV protons
- (2.4-)2.8 m Diameter
- Pulsed beam
- Superconducting (Nb_3Sn)
- 4 tons
- T (extr.)
- Cost?
- Variable-energy possible

Is it worth increasing the field to high values?

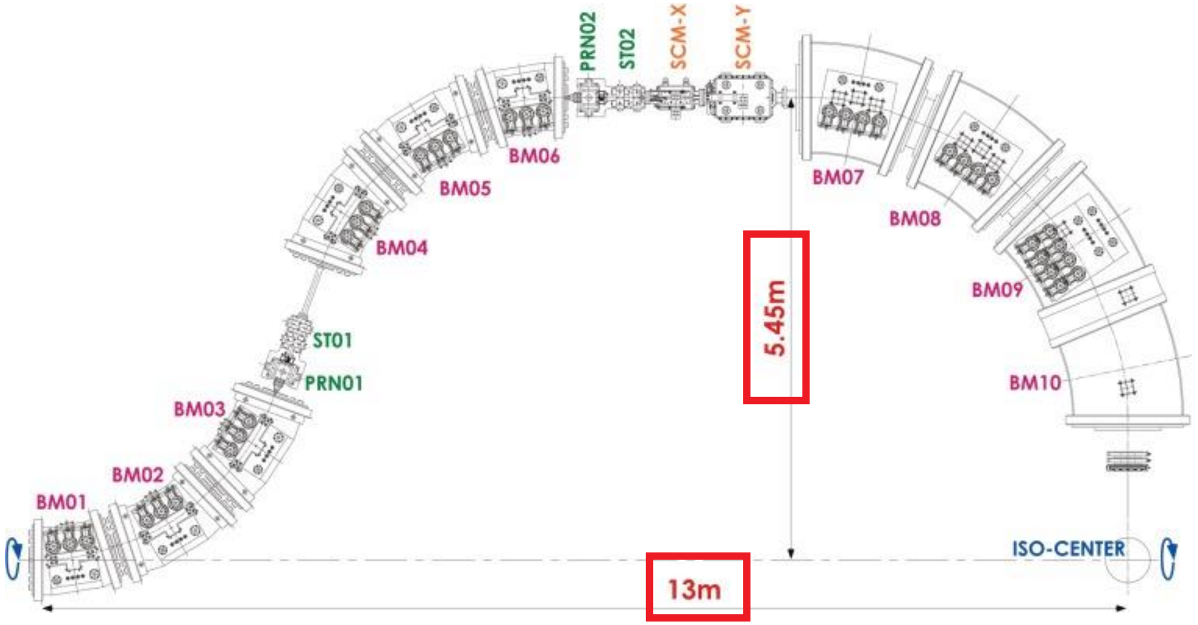
- Lower weigth helps but is not always an issue (i.e. iron is cheap), as long as you stay within certain limits
- Size matters: facility footprint vs. accelerator complexity (turn sep.)

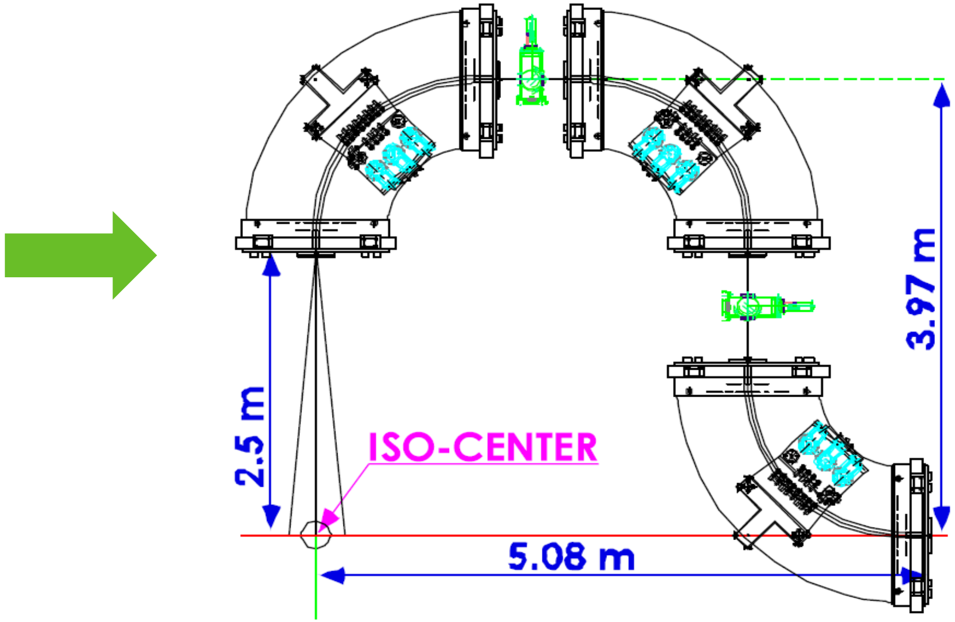




Smaller Gantries (carbon)

- Further size reduction (despite downstream scanning: almost smaller than Pronova proton gantry! At high field and same scanning option… SAD sets system size)
- Less cryogenics needs (from 34 to 9-12 cryocoolers)

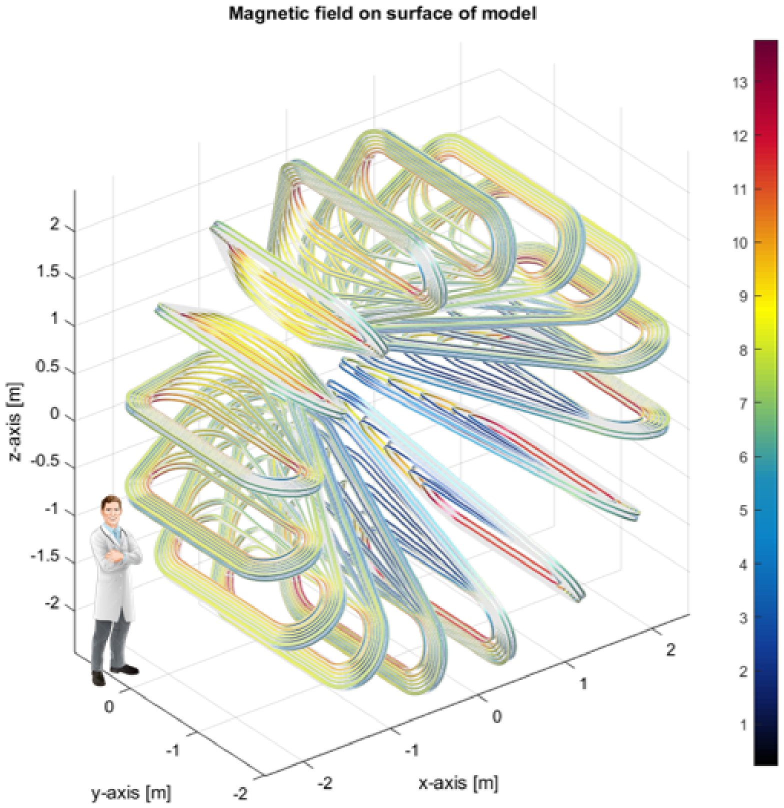




Iwata et al. – IEEE trans on appl. Sup. vol 26, June 2016

NB: remember carbon is even more of a niche than PT, with mostly research institutes involved…

GaToroid for C-ions



- Number of coils: 16 (-)
- Ampere-turns: 3 (MA-turns)
- Peak Field on coil: 13.8 (T)
- Coil dimension: ~3 x 2 (m x m)
- Torus dimensions: ~3 x 5 (m x m)
- **Estimated mass: ~50 (tons)**
- Total Stored energy: 370 (MJ)
- Operating current: 6 (kA)
- J_E = 200…300 (A/mm²)
- Coil Inductance: 0.3 (H)

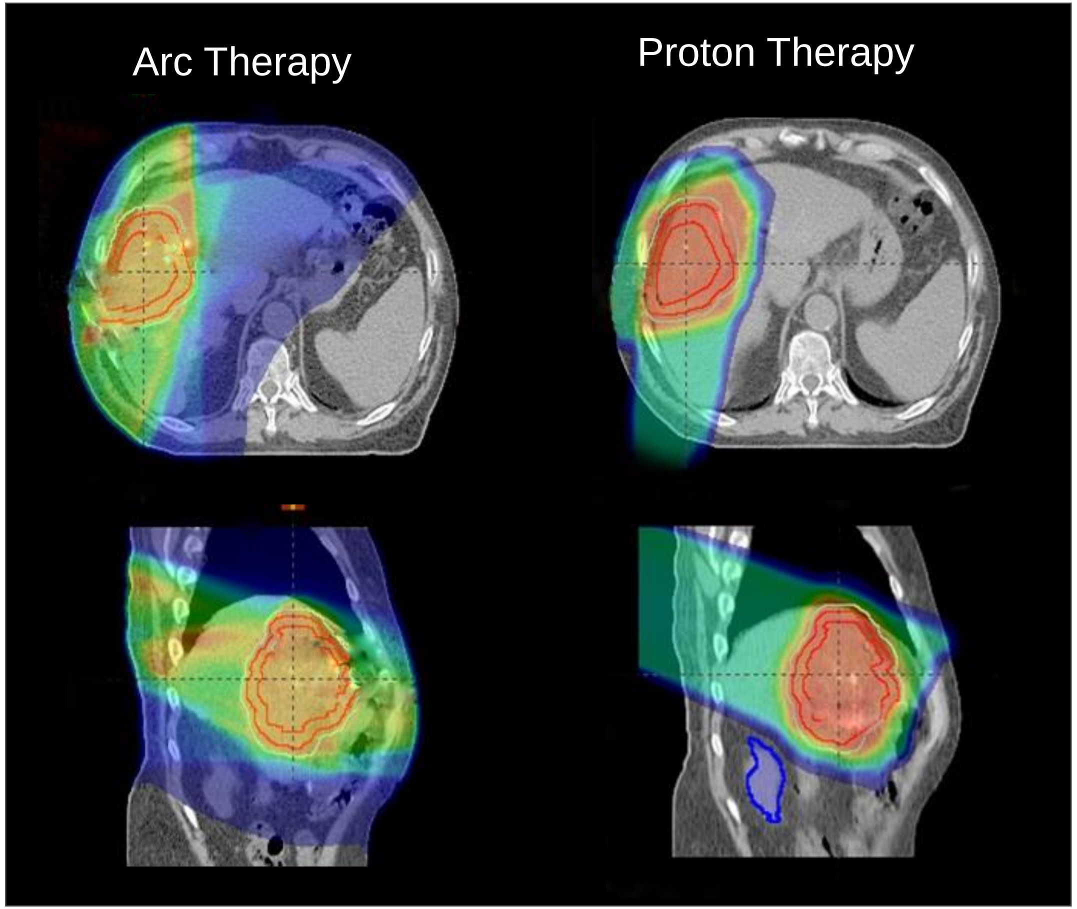
- Operating Temperature
  - 4.5 K (LTS)
  - 10 K (HTS)

There is quite some work to be done here…

Most Exciting things today in PT

- Cost and adoption => Model-based approach
- Better sparing of healthy tissues => Arc Therapy and/or Flash

Irradiation of surrounding tissues - Hepatocellular carcinoma



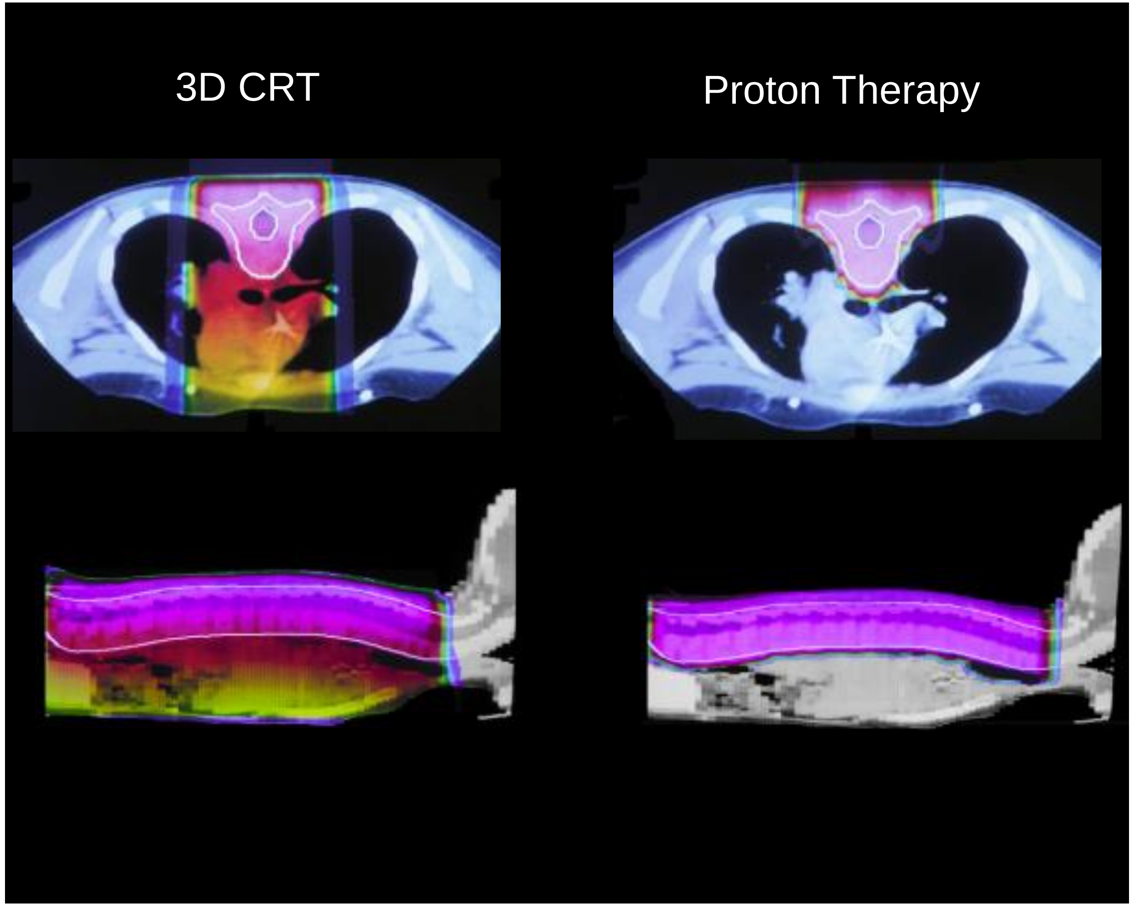
Dose to critical Tissues (mean dose)	Photons	Protons
Right Kidney	20 Gy	0.1 Gy
Lung	12.5 Gy	8.5 Gy

“PBT was found to be a safe and effective local-regional therapy for inoperable HCC. A randomized controlled trial to compare its efficacy to a standard therapy has been initiated” (*)

Images Courtesy of Stefan Both, Ph.D -- PENN Radiation Oncology

(*) Bush DA, et al., « *The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial.* » *Cancer.* 13 (2011) 3053

Pediatric medduloblastoma – Side effects (NTCP)



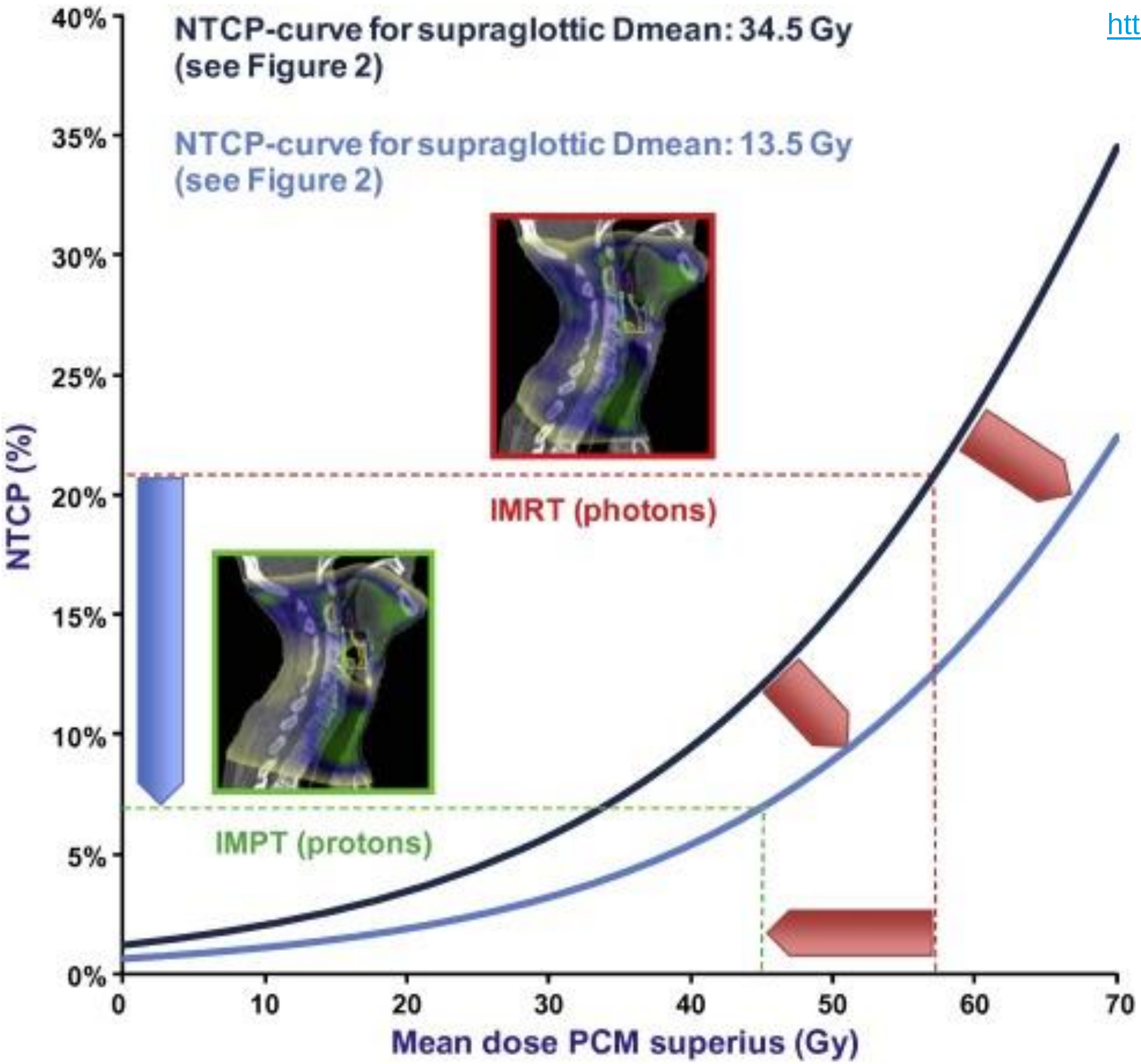
Side Effects	Protons	Photons
Restrictive Lung Disease	0%	60%
Reduced exercise capability	0%	75%
Abnormal EKGs	0%	31%
Growth abnormality	20%	100%
IQ drop of 10 points at 6 yrs	1.6%	28.5%
Risk of IQ score < 90	15%	25%

"Proton beam therapy has become a standard of care for pediatric cancers… " (*)

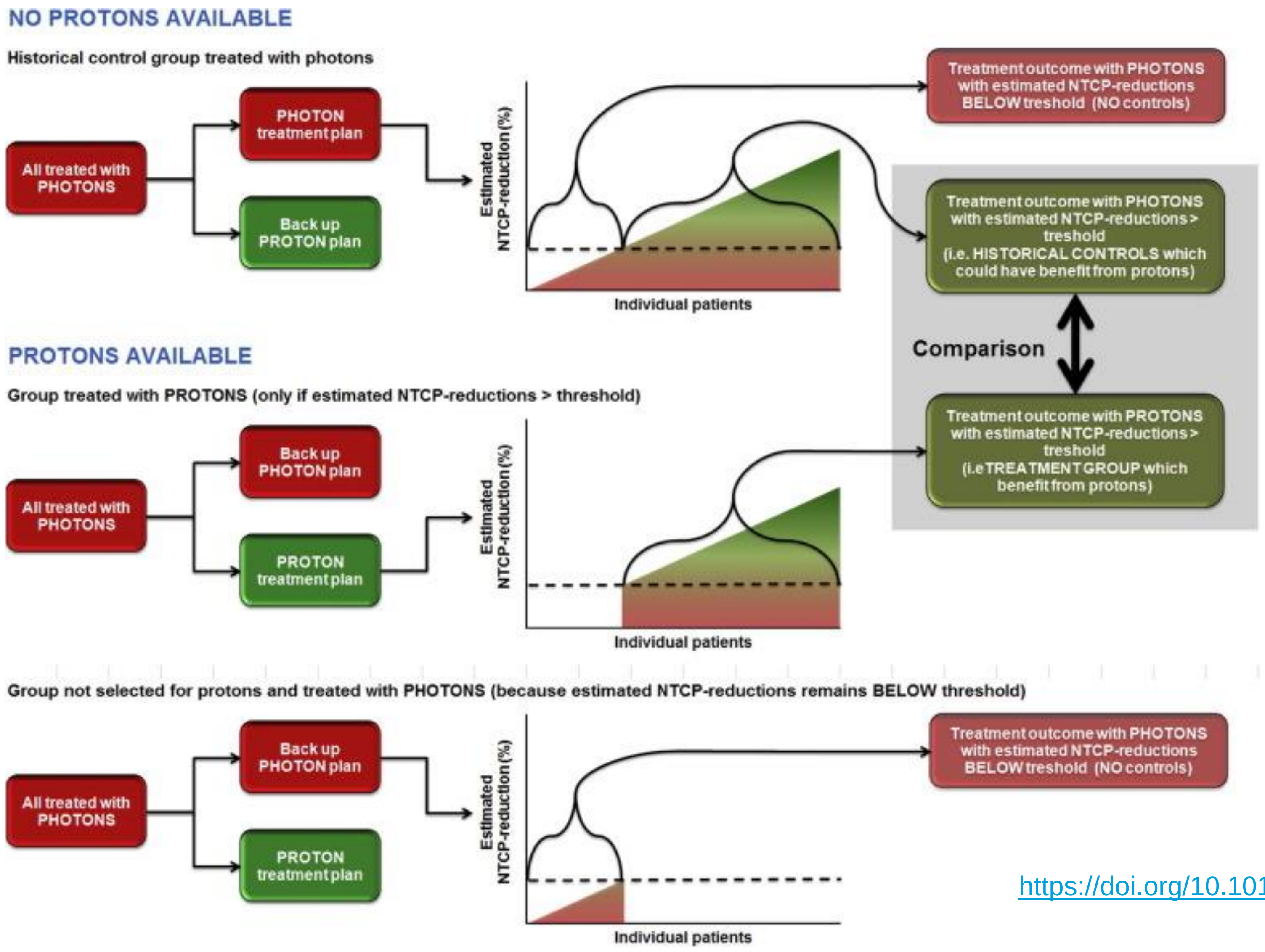
(*) Presentation Dr. Jay S. Loeffler, NPTC/MGH,

Adoption => Model-based approach

https://doi.org/10.1016/j.radonc.2013.05.007

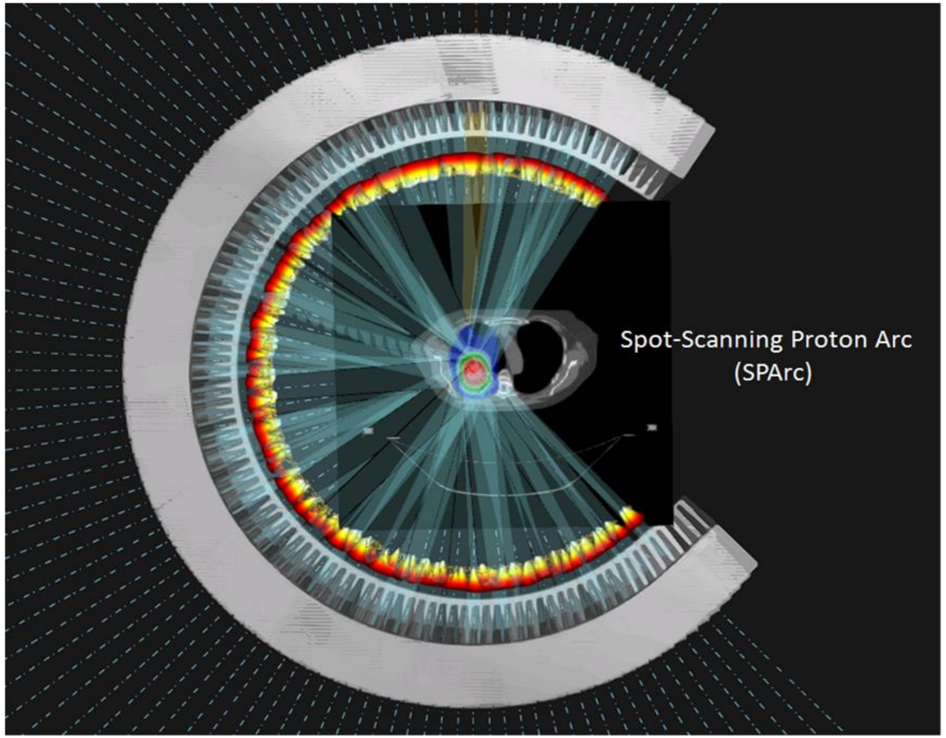


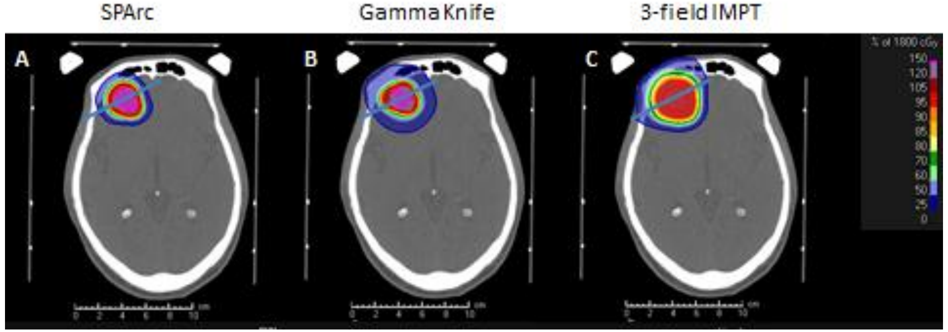
Adoption => Model-based approach



https://doi.org/10.1016/j.radonc.2013.05.007

Trends in PT - Proton Arc therapy





Brain SRS

- Spot-Scanning Proton Arc therapy
  - Enhances dose conformity at the tumor level
  - Reduces the total dose received by the patient
  - Increases the robustness of the treatment plan
  - Improves the adoption of dose escalation and hypo-fractionation
- Proton Arc therapy proof of concept
  - In collaboration with Beaumont Health Proton Therapy Center in Royal Oak, Michigan. Plan delivered in August 2018

First irradiation of a proton ARC beam

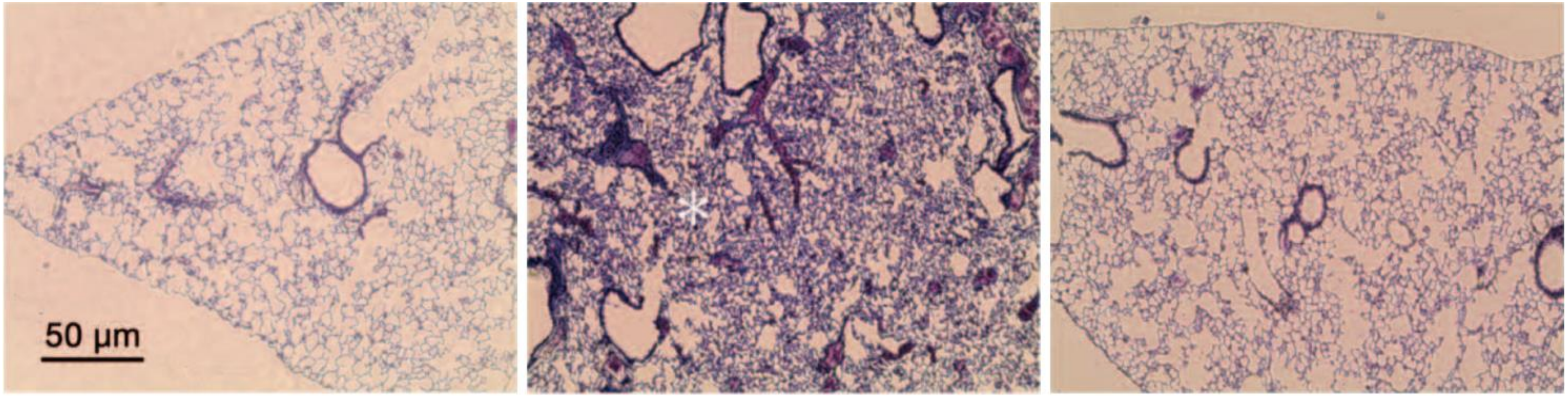
- World première in proton therapy
- Plan delivered in August 2018

THE FIRST IRRADIATION OF A PROTON ARC BEAM

In collaboration with Beaumont Health Proton Therapy Center

Beaumont

Trends in PT - Flash Therapy: less toxicity to healthy tissues



Normal Tissue	Standard RT – 17 Gy	Flash – 17 Gy
0 Gy/s	0.03 Gy/s	60 Gy/s

- Flash could allow dose escalation with less complications
- IBA's equipment is Flash ready
- IBA is the only company to have demonstrated Flash compatible dose rate in a clinical environment (at UMCG in Groningen on March 1 2019 AND in Reading on June 8 2019 – videos on Youtube)

	HL-LHC	FCC-hh	Kiube	Cyclone 70	Cyclone 230	S2C2
Beam energy (TeV)	7	50	1,80E-05	7,00E-05	2,30E-04	2,30E-04
circumference (km)	26,7	100	6,00E-03	1,20E-02	1,40E-02	8,00E-03
Dipole field (T)	8,33	16	1,3	1,1	3	5,7
Injection energy (TeV)	0,45	3,3	1,00E-08	4,00E-08	1,00E-08	1,00E-08
Transverse normalized emittance (µm)	2,5	2,2	~1,2	~8,7	~18	~60
beam current (A)	1,12	0,5	3,00E-04	7,50E-04	5,00E-07	1,50E-07
RMS IP spot size (µm)	7,1	6,8	2000	2000	3000	3000

Radiopharmaceuticals

RadioPharma Solutions

Tailor made radiopharmaceutical production centers

SYNTHERA®

CYCLONE® **KIUBE**

INTEGRALAB®

500

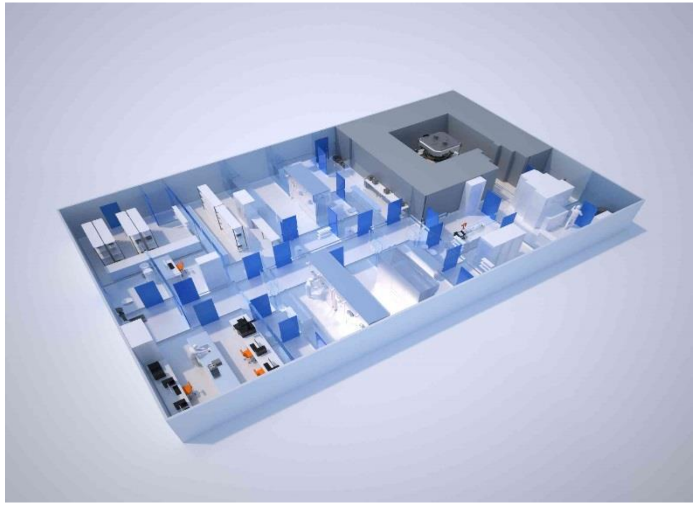
More than 500 Synthera worldwide

260

Cyclotrons sold

N°1

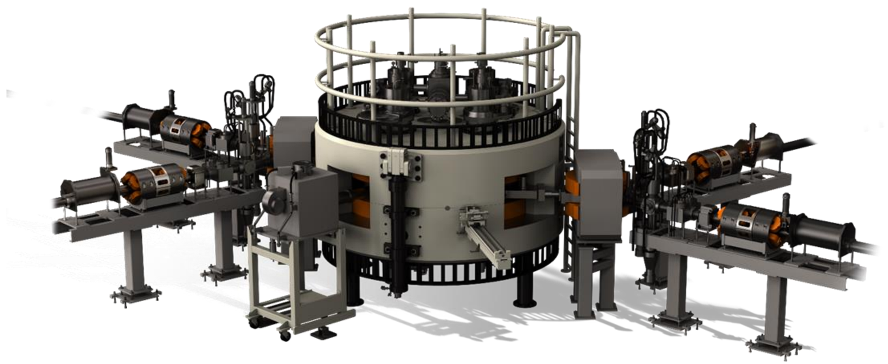
Middle and High energy



RadioPharma Solutions

- New generation Cyclone®KIUBE and Cyclone®70
  - Reach new markets
  - Gain market shares
  - Give access to latest applications (e.g. theranostics)

Cyclone®70

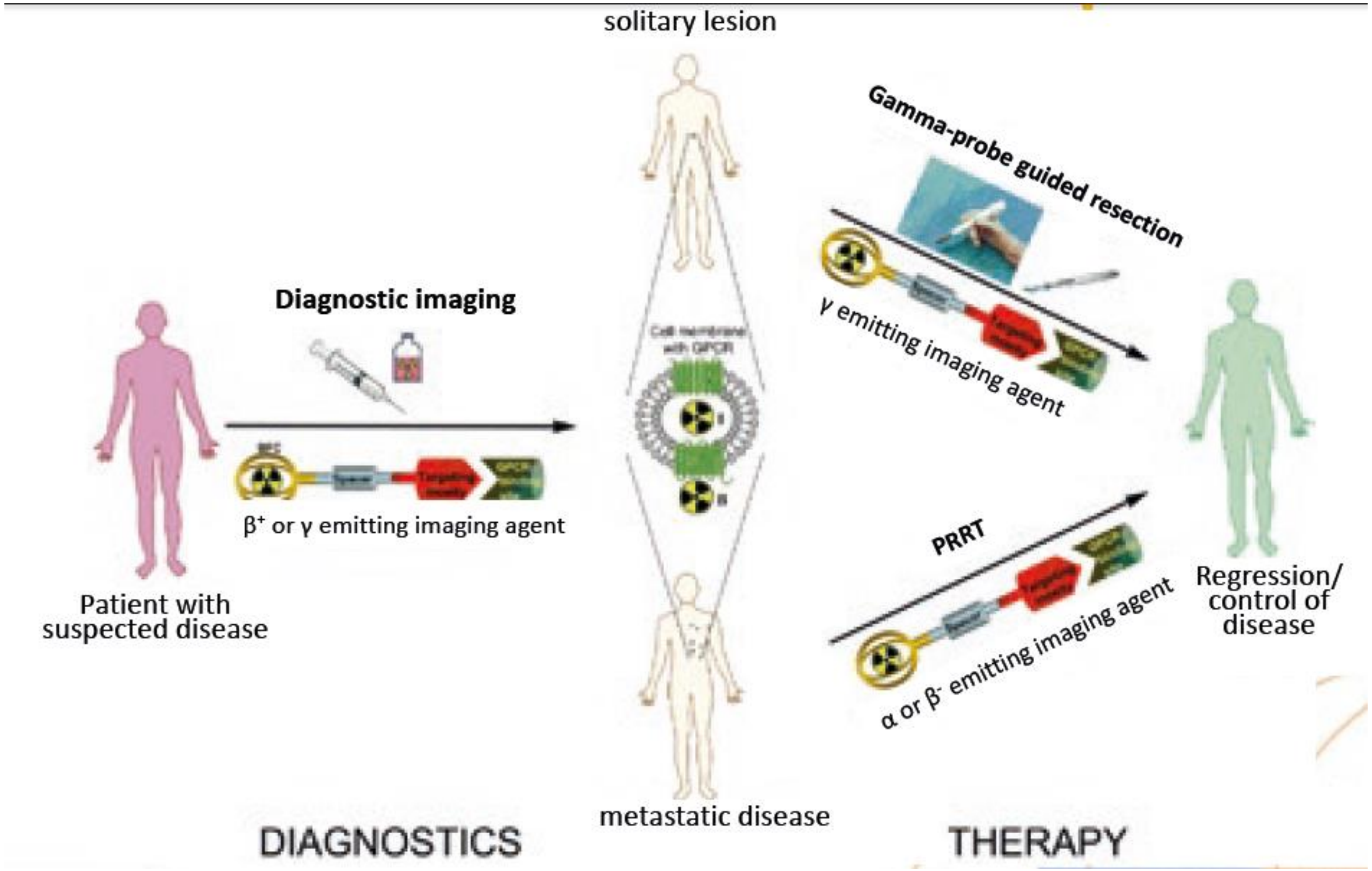


- High energy and high current proton cyclotron
- Production of isotopes for diagnosis of cardiovascular diseases and other critical illnesses

Cyclone®KIUBE

- Highest radiopharmaceuticals production capacity
- Upgradable to enable the increase of production capacity
- Give access to 18F, 13N, 15O, 11C (CO2 & CH4), 18F2, 68Ga,...

Most exciting thing in RPS today: Theranostics



- Is there a tumor?
- Is is solitary or metastatic?
- Has the tumor the right receptors for efficient therapy?
- Therapy: same molecule with therapy isotope.

Exciting for IBA: Cyclotron or Rhodotron-based Production

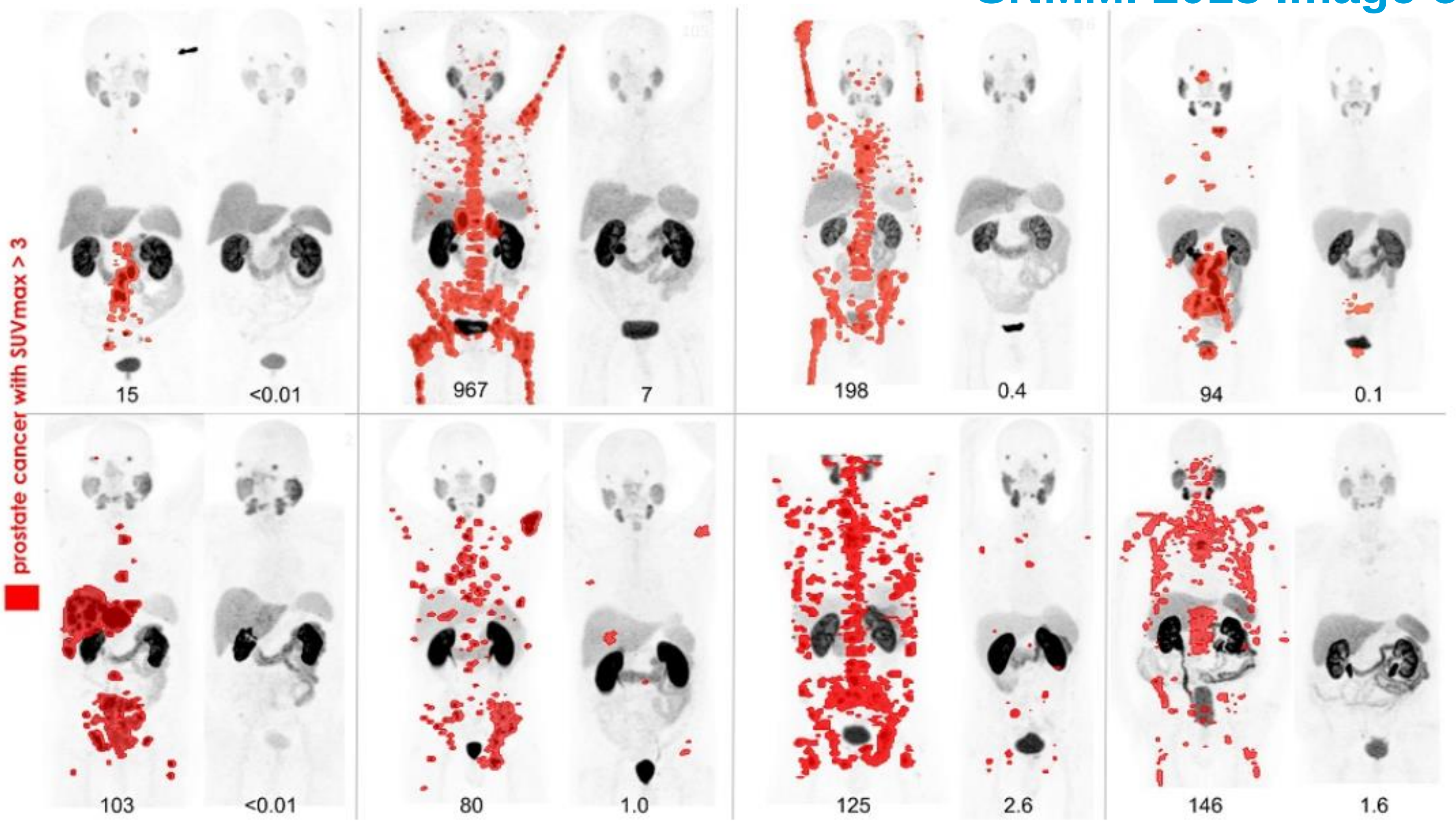
Radiometals

Radionuclide	Half life (h)	Mode (keV)	Production	Chelator	Diagnostic match	Half life (h)	Production
^{90}Y	64.1	β^- (934)	Generator	DTPA (tiuxetan) DOTA	^{68}Ga ^{86}Y ^{111}In	1.13 (PET) 14.7 (PET) 67.9 (SPECT)	Generator Cyclotron Cyclotron
^{177}Lu	161	β^- (134) γ (112, 208)	Reactor	DOTA	^{68}Ga ^{111}In	1.13 (PET) 67.9 (SPECT)	Generator Cyclotron
^{67}Cu	61.9	β^- (141) γ (91, 93, 185)	Cyclotron	NOTA NODAGA TETA CPTA (DOTA) cross-bridged macrocycles	^{64}Cu ^{62}Cu ^{61}Cu	12.9 (PET) 0.16 (PET) 3.3 (PET)	Cyclotron ~~(Generator)~~
^{47}Sc	80.4	β^- (162) γ (159)	Various	DOTA AAZTA DO3AP	^{86}Y ^{43}Sc ^{44}Sc	14.7 (PET) 3.9 (PET) 3.97 (PET)	Cyclotron Generator

Adapted after Müller C, van der Meulen NP, Benešova M et al. J Nucl Med 2017; 58:91S–96S

« Exciting » for the Patient: Prostate caner

SNMMI 2018 Image of the year



^{68}Ga-PSMA PET before and after ^{177}Lu PSMA617 theranostic in 8 patients with metastatic prostate cancer

	LEP2	FCC-ee	TT50	TT1000	TT300HE
Beam energy (GeV)	104	175	1,00E-02	8,00E-03	4,00E-02
circumference (km)	26,7	100	5,60E-03	1,00E-02	9,00E-03
H-V transverse normalized emittance (pm)		1,3-0,0025	1,93E+05		2,58E+05
beam current (mA)	3,04	6,6	2	100	3
H-V RMS IP spot size (µm)	182-3,2	36-0,07	5000-10000	5000-10000	5000-10000

Industrial Solutions

Industrial Solutions

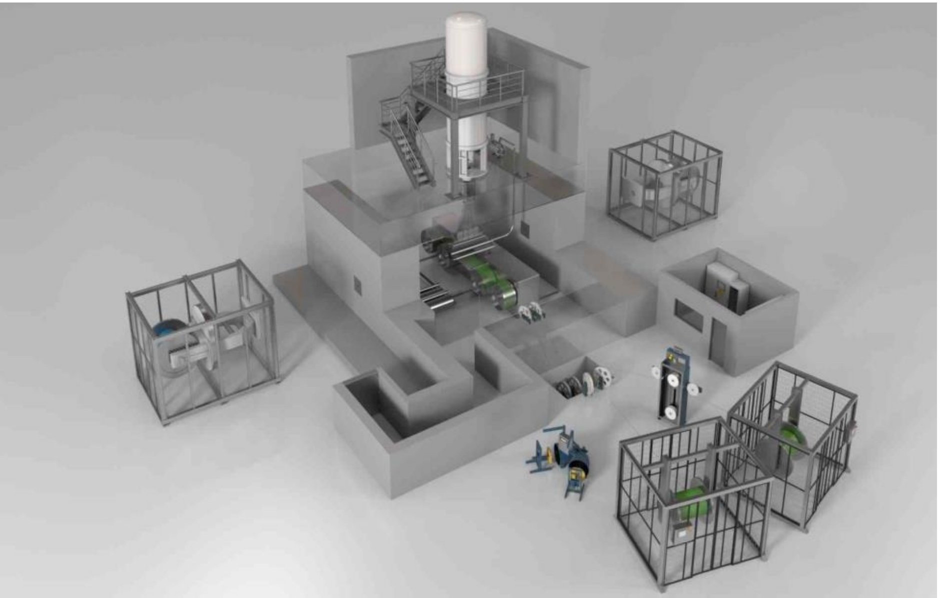
Sterilization and polymer improvement solutions

RHODOTRON®

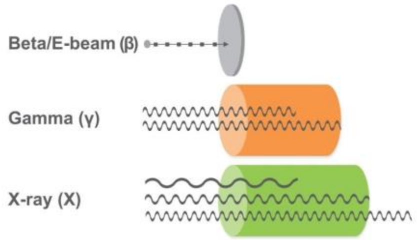
DYNAMITRON®

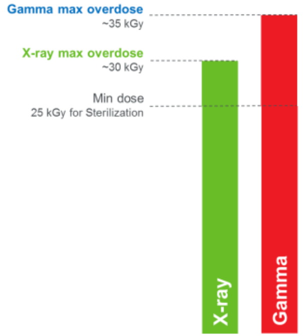
World
N°1

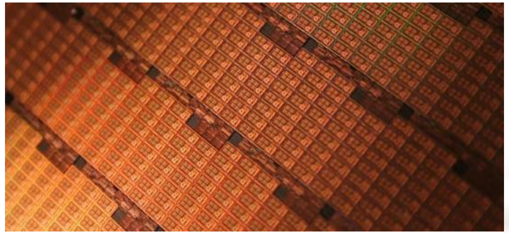
250
IBA Industial accelerators

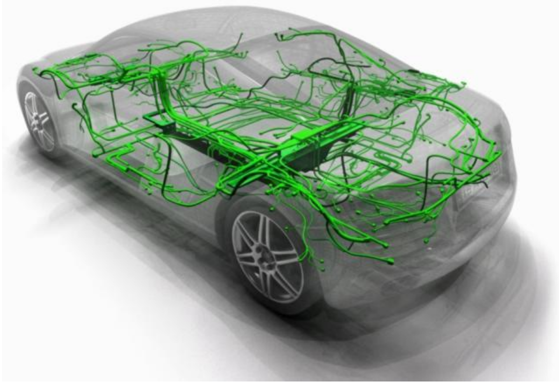


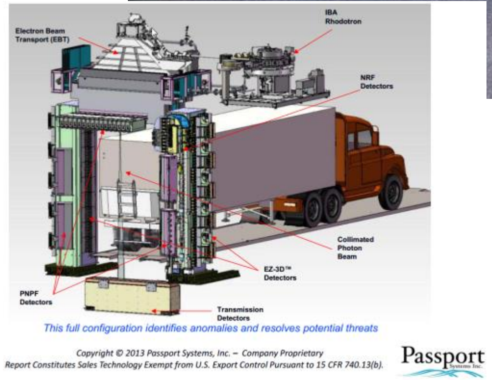
Applications











Exciting stuff in these applications

Well, maybe there are too many exciting tings, and it is sometimes hard to distinguish what will become big or not

But:

- Variety in applications

⇒Accelerator versatility

  - Energy
  - Current
  - Beam lines

The Rhodotron

- CEA patent brought to market by IBA
  - From the TT50 (20 kW, 10 MeV)
  - To the TT1000 (800 kW, 7 MeV)
  - To the TT300HE (120 kW, 40 MeV)
- Pulsed operation for energy-saving

New TT50

Sterilization
Research
New Applications

TT100

Sterilization
Low volumes

TT200/TT300

Sterilization
High
throughputs

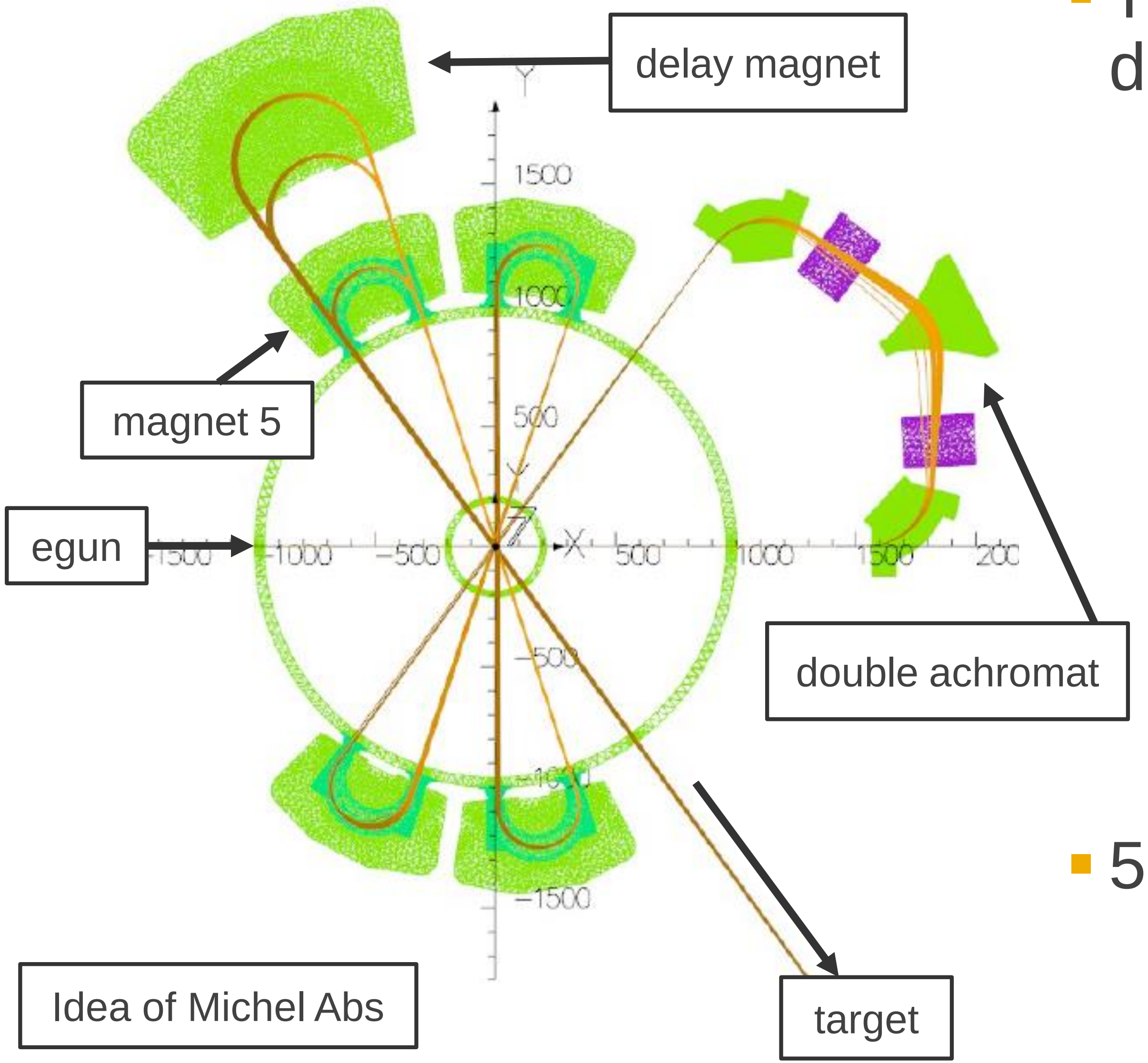
TT1000

Sterilization
Very High
throughputs

High Energy

Radio-Isotopes
And Theranostics
Production

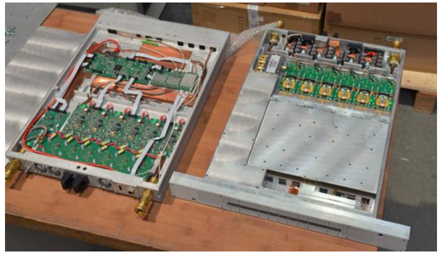
Felxibility: Energy

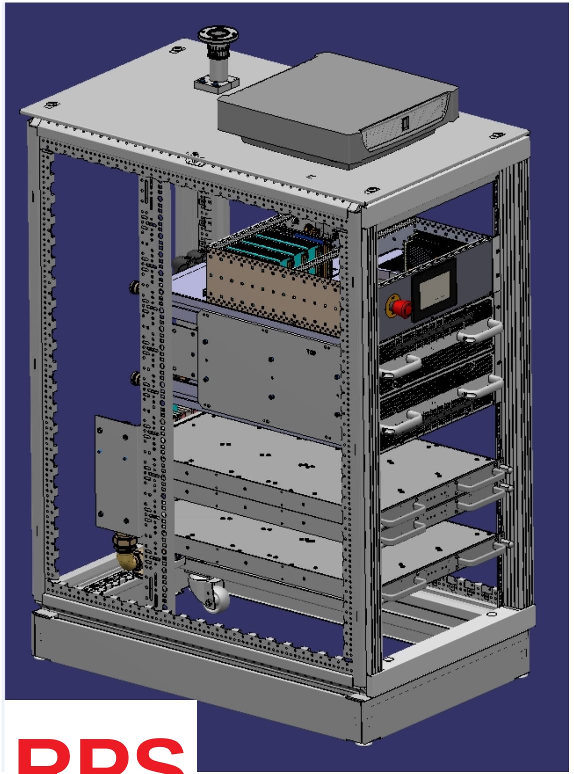


- This layout allows to extract two different energies onto one same target
  - first 4 passes accelerate upto 5.8 MeV
  - magnet 5 on
    - ⇒ last pass accelerates up to 6.96 MeV
  - magnet 5 off :
    - ⇒ beam passes through delay magnet
    - ⇒ the beam is reinjected into the same final pass but the RF-phase is shifted
    - ⇒ last pass can accelerate (1.16 MeV) or decelarate **or anything in between** depending on the position of the delay magnet
    - two solutions exist for each extraction energy
- 5 MeV layout may replace dynamitron

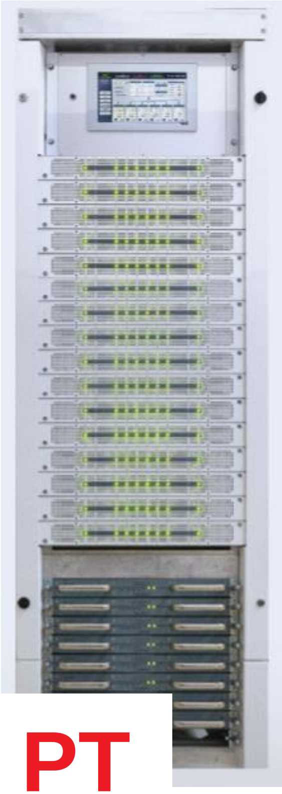
Flexibility: Beam Power => Solid-State RF amplifiers

- Frequencies: 40, 106, 176, 352 MHz
- Power: from 10 kW to…



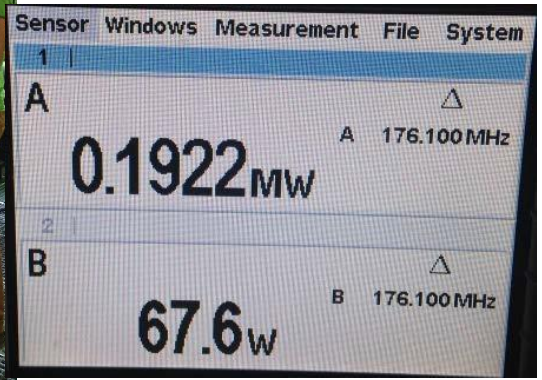


RPS



PT

Myrrha



IBA strong purpose – 5 stakeholders

Affordability
Treatment & Process Quality
Innovation
Customer Satisfaction

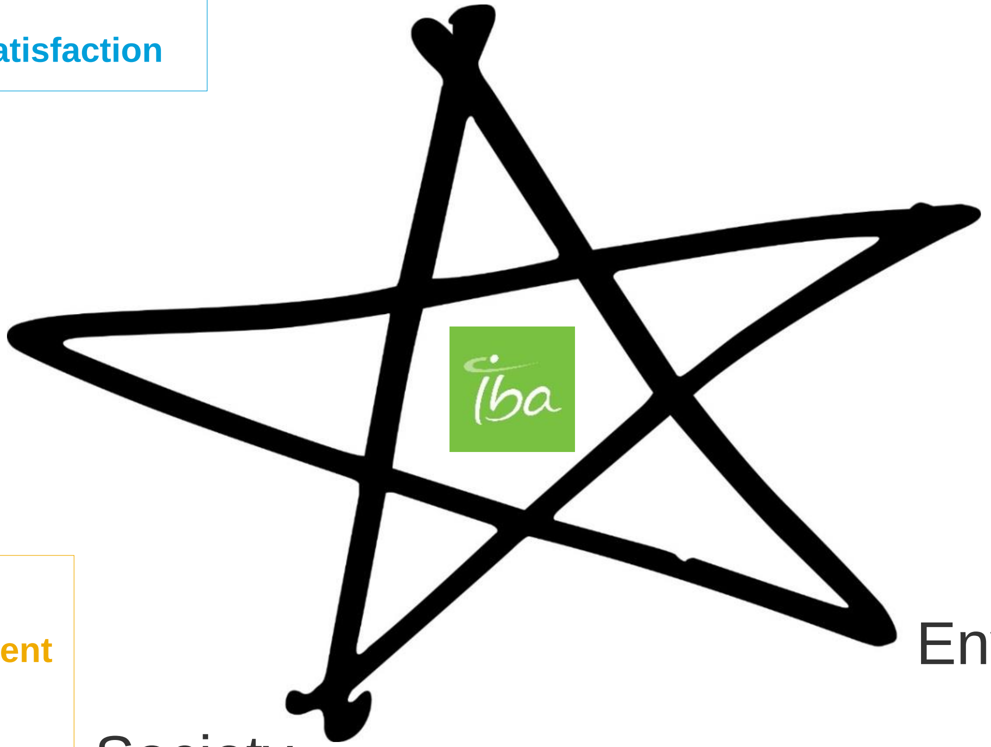
Patients & Customers

Profitability
Ownership & Independence
Access to *good* capital

Shareholders

Quality Jobs
The Promise
Health & Safety

People



Climate Change
Waste
Mobility
Resources scarcity

Environment

Business Ethics
Responsible Procurement
Education
Community involvement

Society

Protect, Enhance and Save Lives

Thank you

(and if you happen to come back to Belgium, come and visit us…)

Viggo Mommaerts, treated with Proton Therapy