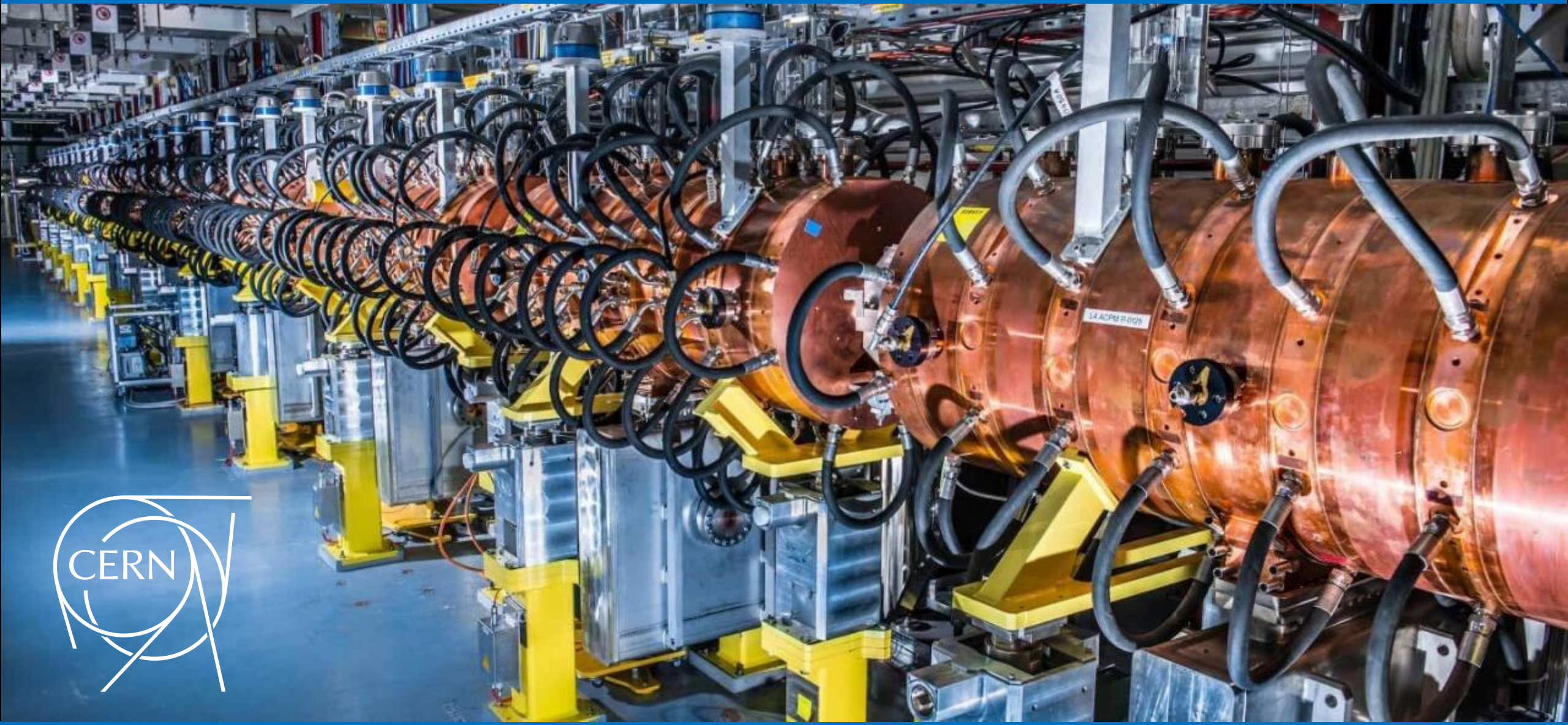
Maurizio Vretenar CERN

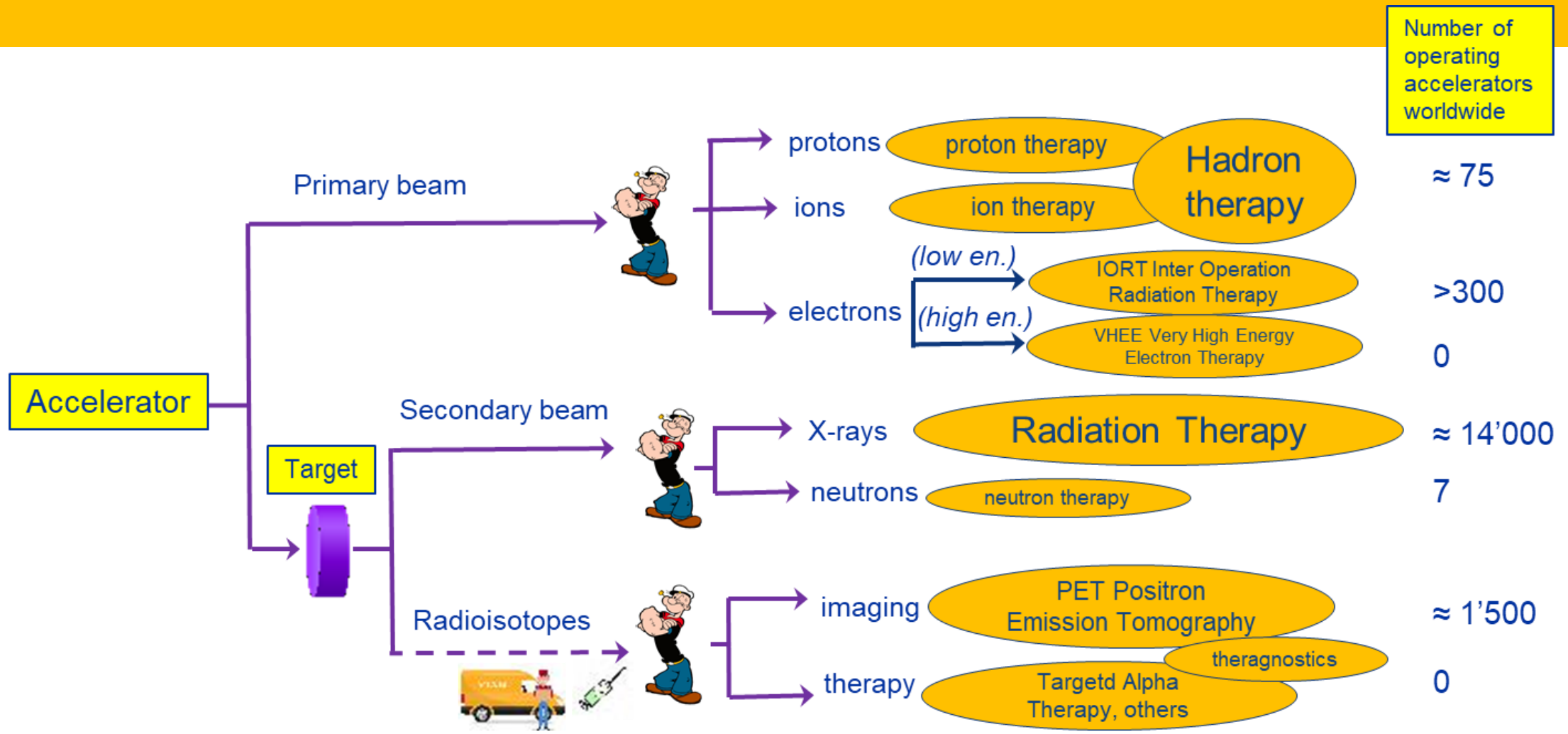
LECTURE 8

RTU/CERN May 2022



Accelerators for Medicine

Accelerators for medicine



Total: ≈ 16'000 particle accelerators worldwide operating for medicine

The healthcare potential of accelerators

- All these systems share the vision of a **bloodless surgery and imaging**: penetrate into the human body to treat diseases and to observe internal organs without using surgical tools.
- Particle beams (primary and secondary) precisely deliver large amounts of energy to small volumes, penetrate in depth (**different from lasers**) and interact with cells, molecules, and atoms (electrons and nuclei).
- Particles beams can activate the nuclei generating radiation that can destroy cancerous cells or can be detected from outside.

For a U.S. population of over 300 million people, there are some 16 million nuclear medicine procedures per year.

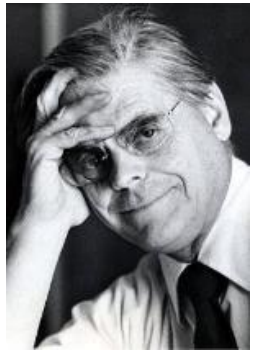
Nuclear medicine:
application of radioactive substances in the diagnosis and treatment of disease

Radiation therapy:
therapy using ionizing radiation, generally as part of cancer treatment to control or kill malignant cells

Medicine at the first accelerators

The idea of using accelerators for treating diseases is almost as old as accelerators

- After the cyclotron invention in 1936, the new Berkeley 37-inch cyclotron was producing isotopes for physics, biology and medicine – in parallel to the time devoted to discoveries in nuclear physics.
- Starting in 1937, Lawrence's brother John was the pioneer of injecting radioisotopes produced at the cyclotron to cure leukemia and other blood diseases.
- In 1938 starts direct irradiation of patients with neutrons from the new 60-inch cyclotron.
- In 1946, Robert Wilson proposed to use protons to treat cancer, profiting of the Bragg peak to deliver a precise dose to the tumour.
- First treatment of pituitary tumours took place at Berkeley in 1956.
- First hospital-based proton treatment center at Loma Linda (US) in 1990.



Lawrence's priority was to promote his science and to build larger and larger cyclotrons. He considered medical applications as a formidable tool to show the public the potential of this new technology and to raise more funding for his projects.

During the 30's, more than 50% of beam time was devoted to producing isotopes for medicine and other applications, to the disappointment of the physicists that were using the cyclotron beams to lay the ground of modern nuclear physics.

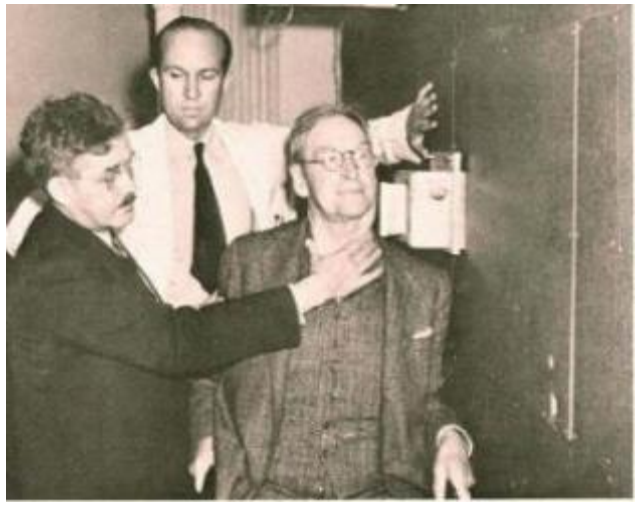
Modern accelerators for cancer treatment and isotope production

There are today about 16’000 accelerators in hospitals or working for hospitals, complex devices that have specific requirements, somehow different from a scientific accelerator:

- The beam must be perfectly known, stable and reliable.
- The accelerator (as the radiopharmaceutical unit in case of production of isotopes) have to follow strict Quality Assurance procedures.

Example: factor 4 in the complexity and cost of the control system for a medical accelerator as compared to a scientific one.

The role of the medical physicist is essential in planning the treatment and in guaranteeing the delivered dose.

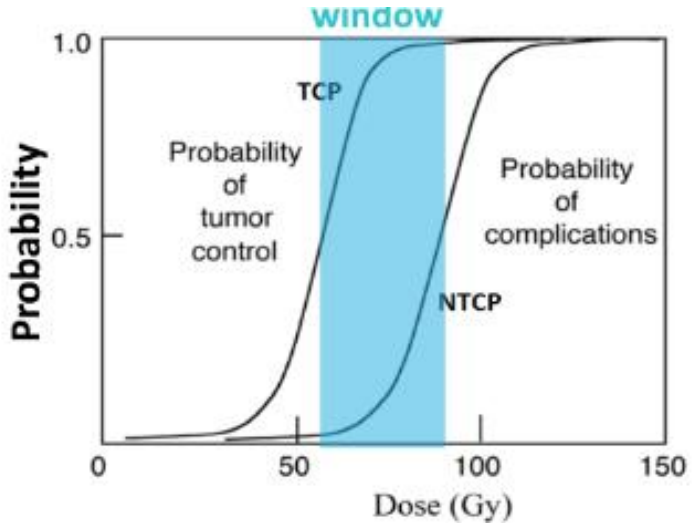


From the early tests at Lawrence’s cyclotron to a modern treatment room at CNAO

Medical exposure – a critical issue

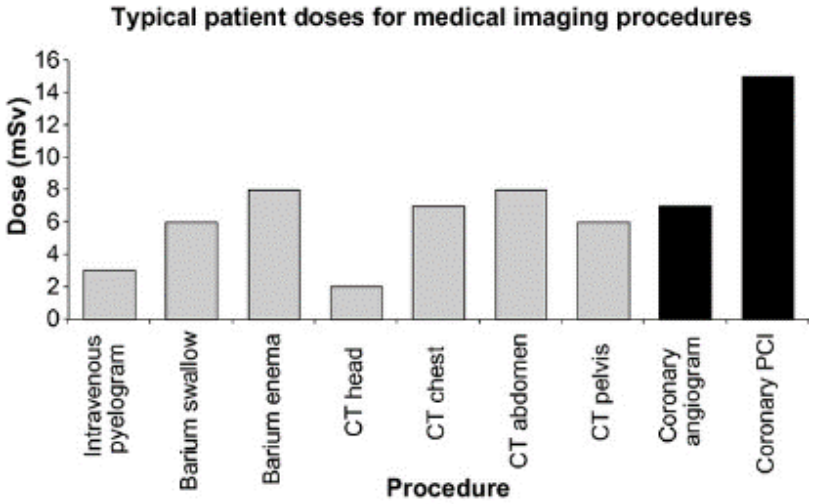
TCP=Tumor control probability
NTCO=normal tissue complication probability

Radiation management and control is a key issue in nuclear medicine.
- important doses are delivered to patients (comparison risk-benefit)
- the dose to medical personnel is subject to strict legal limits.



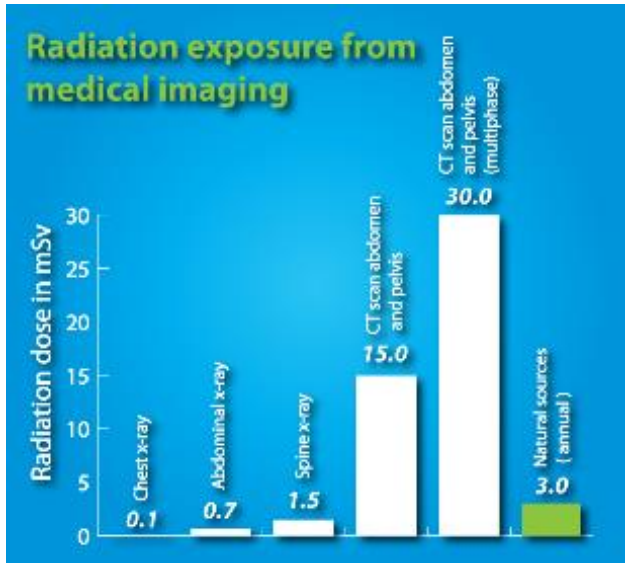
CERN limits

	Area	Dose limit [year]	Ambient dose equivalent rate	
			Work place	Low occupancy
	Non-designated	1 mSv	0.5 µSv/h	2.5 µSv/h
Radiation Area	Supervised	6 mSv	3 µSv/h	15 µSv/h
	Simple	20 mSv	10 µSv/h	50 µSv/h
	Limited Stay	20 mSv		2 mSv/h
	High Radiation	20 mSv		100 mSv/h
	Prohibited	20 mSv		> 100 mSv/h



Up to 2000 mSv highly targeted dose in conventional radiotherapy !

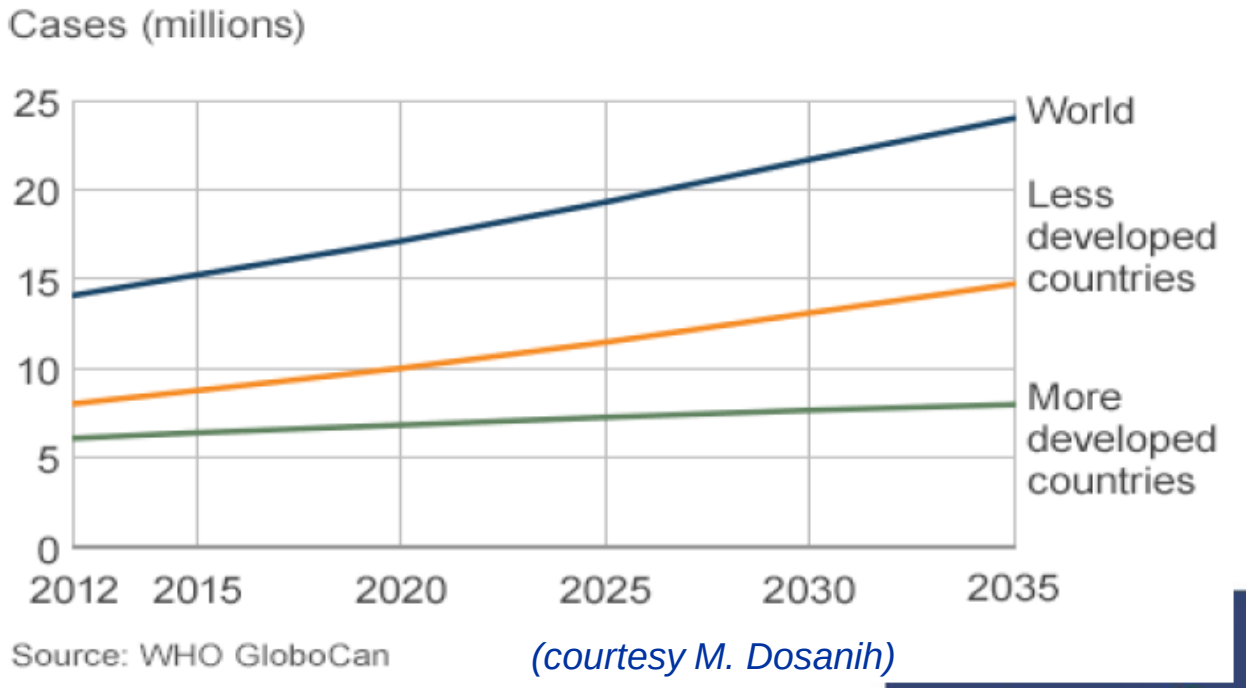
Source: S. Liauw et al., Translational Medicine, 5, 173



Impact of cancer on world population

Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer (WHO).

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012



(courtesy M. Dosanih)

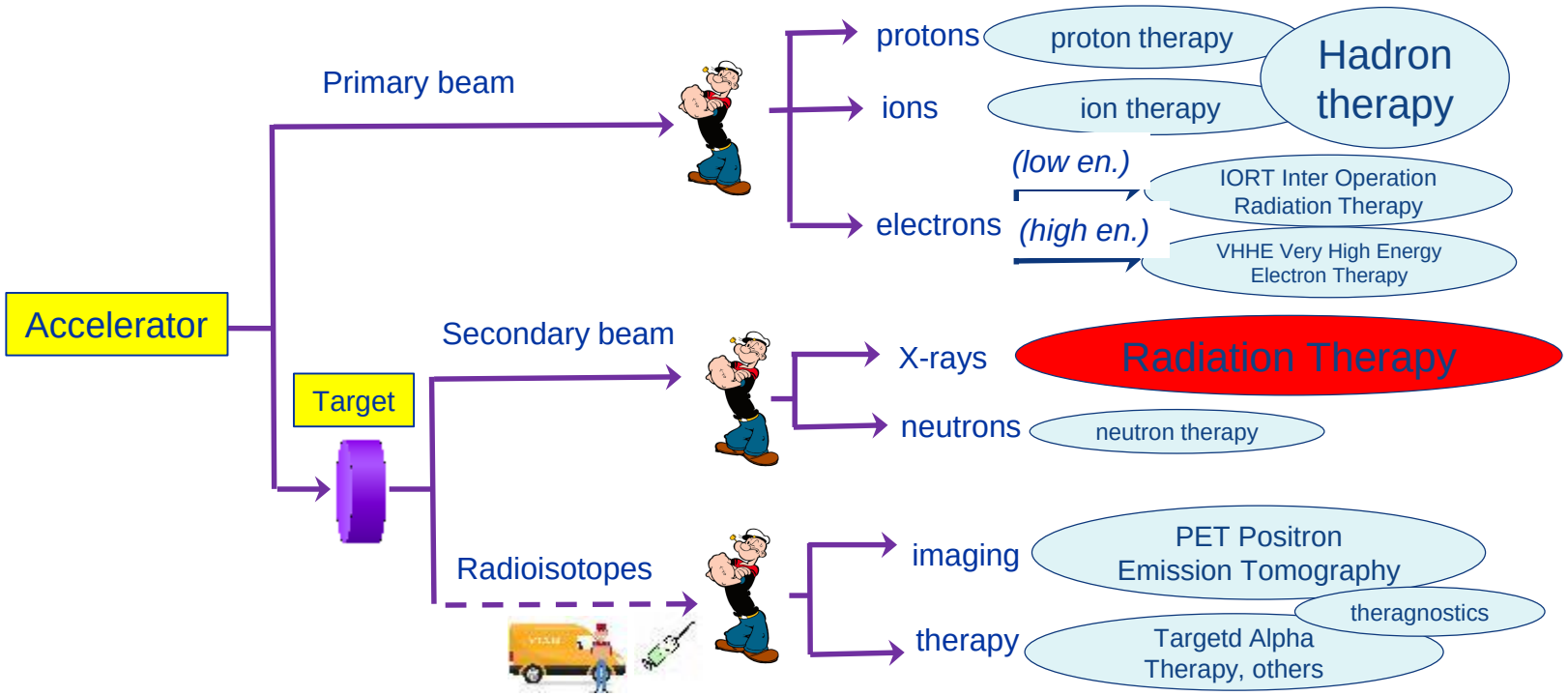
Increase of cancer cases due to:

- Increasing age of population
- Aggressive environmental and living conditions in developing countries.

Nowadays, the standard protocol for treatment of most cancers is based on:

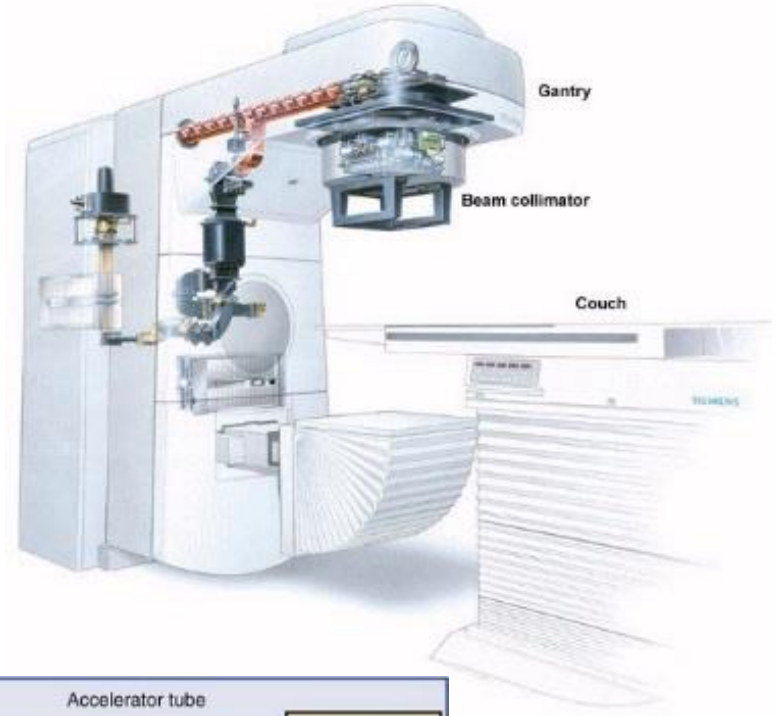
1. Surgery
2. **Radiotherapy** (accelerator-based)
3. Chemiotherapy
4. (Immunotherapy)

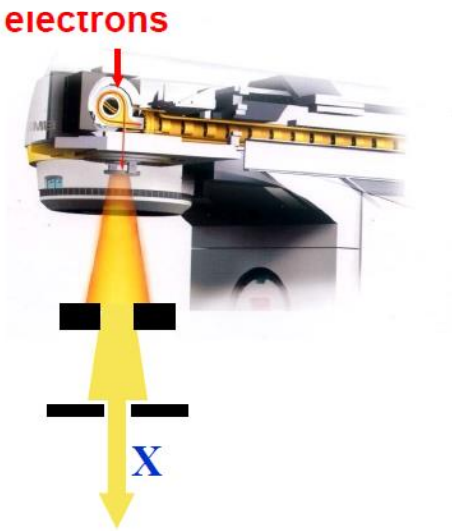
1. Radiation therapy



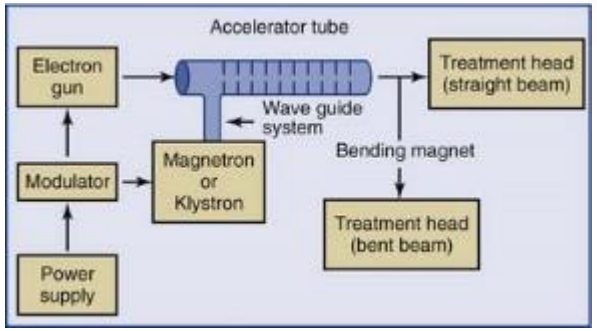
The most successful accelerator

Electron Linac (linear accelerator) for radiotherapy (X-ray treatment of cancer)



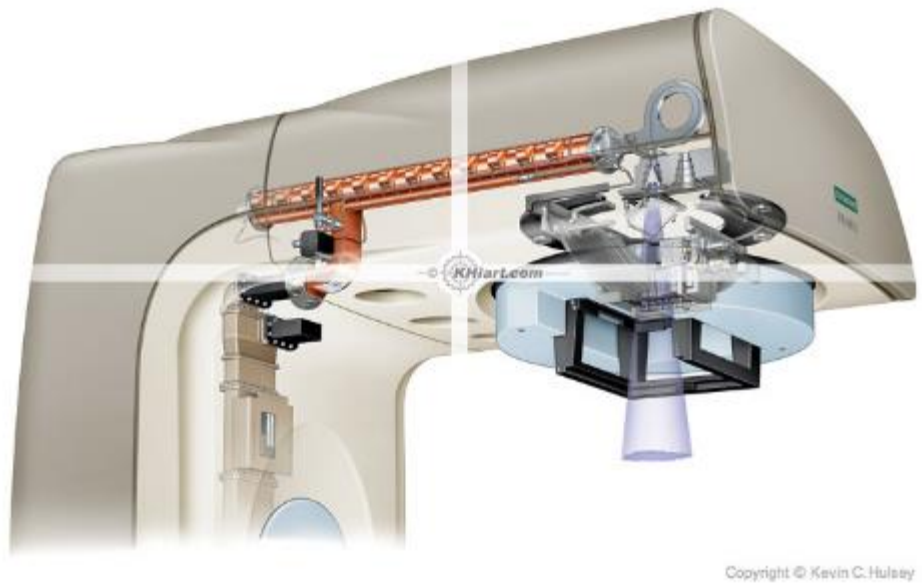


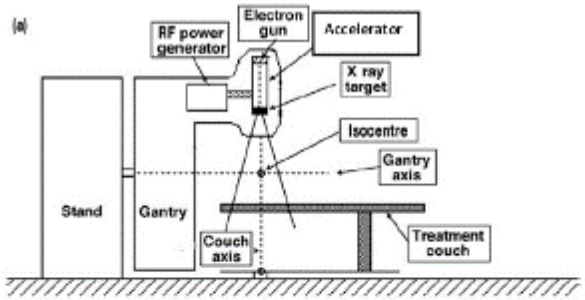
5 – 25 MeV e-beam
Tungsten target

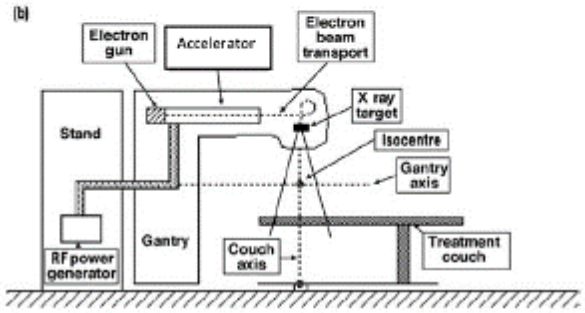


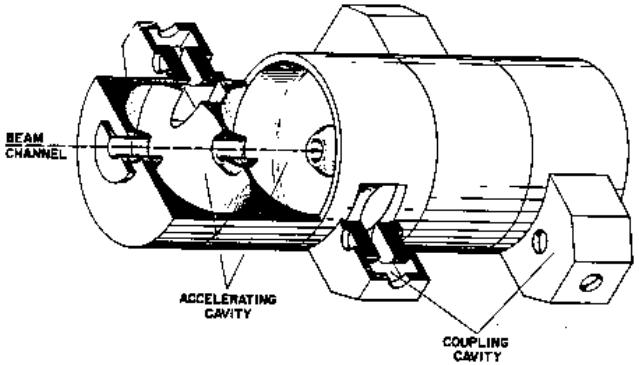
14,000 in operation worldwide!

Inside a radiation therapy linac







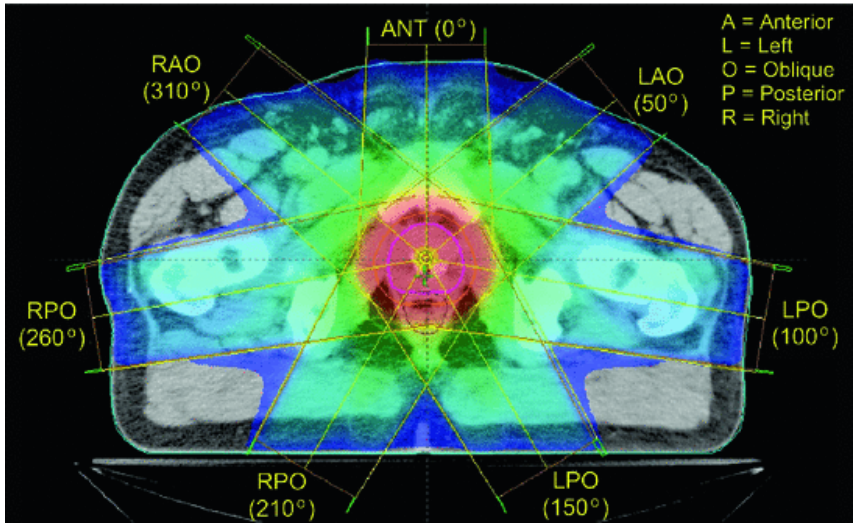


The Side Coupled Linac structure was invented at Los Alamos in the late 60's for the 800 MeV LA meson facility.
Because of its robustness, stability, reliability and low cost since the late 70's it has been used in a 3 GHz version to produce X-rays for radiation therapy

A great example of technology transfer from basic science to society

Modern radiotherapy

X-rays are used to treat cancer since last century. The introduction of the electron linac has made a huge development possible, and new developments are now further extending the reach of this treatment.



Accurate delivery of X-rays to tumours

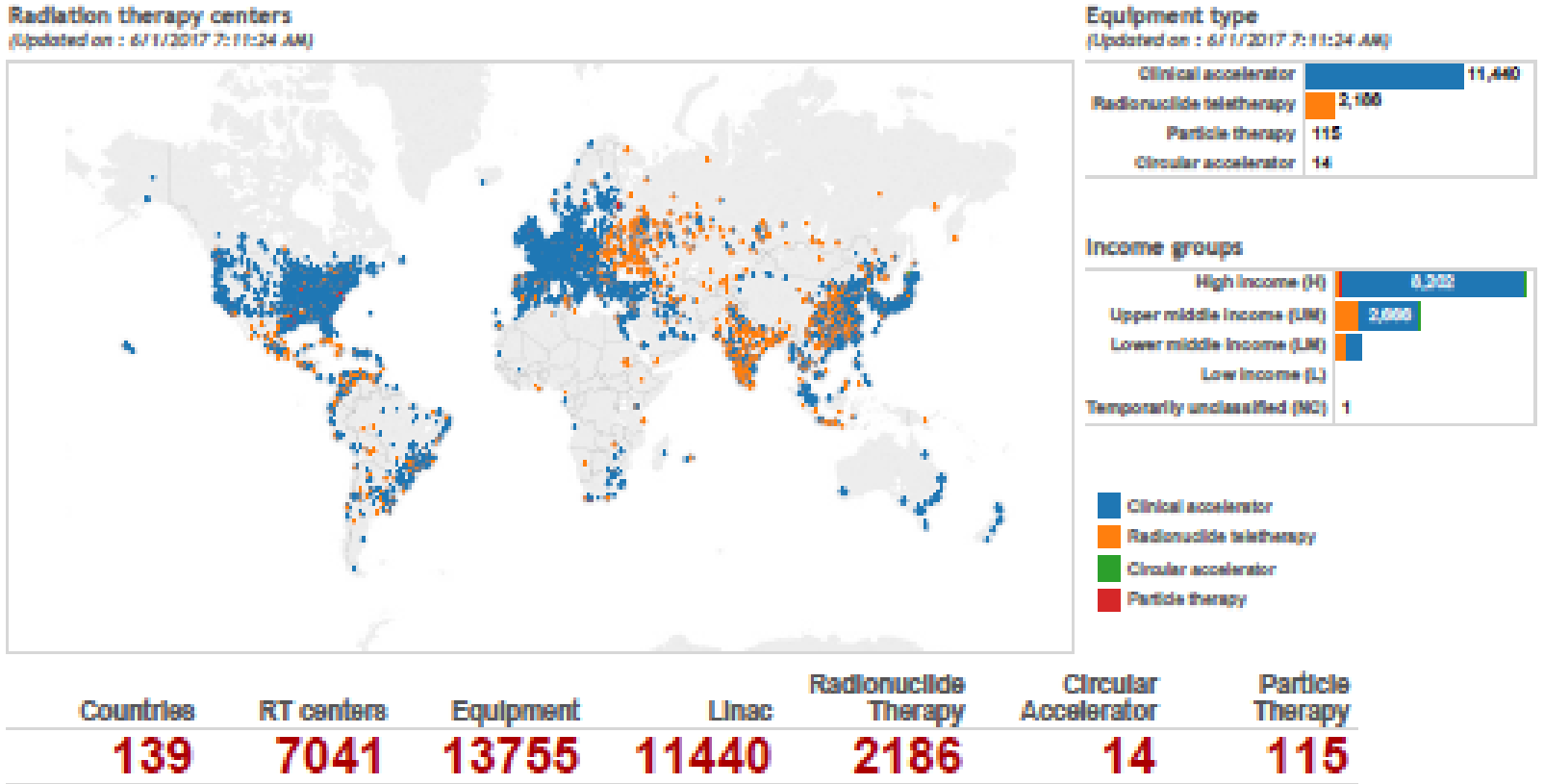
To spare surrounding tissues and organs, computer-controlled treatment methods enable precise volumes of radiation dose to be delivered. The radiation is delivered from several directions and transversally defined by multi-leaf collimators (MLCs).

Combined imaging and therapy

Modern imaging techniques (CT computed tomography, MRI magnetic resonance imaging, PET positron emission tomography) allow an excellent 3D (and 4D, including time) modelling of the region to be treated.
The next challenge is to combine imaging and treatment in the same device.

Fig. 3.4: The MR-linac, developed by Elekta, consists of a linear accelerator equipped with multi-leaf collimator technology for accurate radiotherapy dosage, combined with a high-field MR imaging system. The MR-linac is work in progress and is not available for sale or distribution (courtesy of Elekta).

Radiation therapy worldwide



Countries	RT centers	Equipment	Linac	Radionuclide Therapy	Circular Accelerator	Particle Therapy
139	7041	13755	11440	2186	14	115

(courtesy ENLIGHT Network)

Radiation therapy nowadays relies mostly on linear accelerators, which in developed countries have replaced the old «cobalt bombs».
Many countries with an expected increasing cancer rate are not covered.

The ICEC Initiative for a new linac design

Today the radiation therapy linac market is in the hands of 2 large companies – and two smaller «niche» producers.
Equipment is expensive, requires maintenance and a stable operating environment (electricity, humidity, dust, etc.) → this has reduced the access of low and middle income countries to radiation therapy.

A collaboration led by the NGO International Cancer Expert Corps with the participation of STFC and CERN has started the development of a new radiotherapy linac specifically aimed at low and medium income countries.

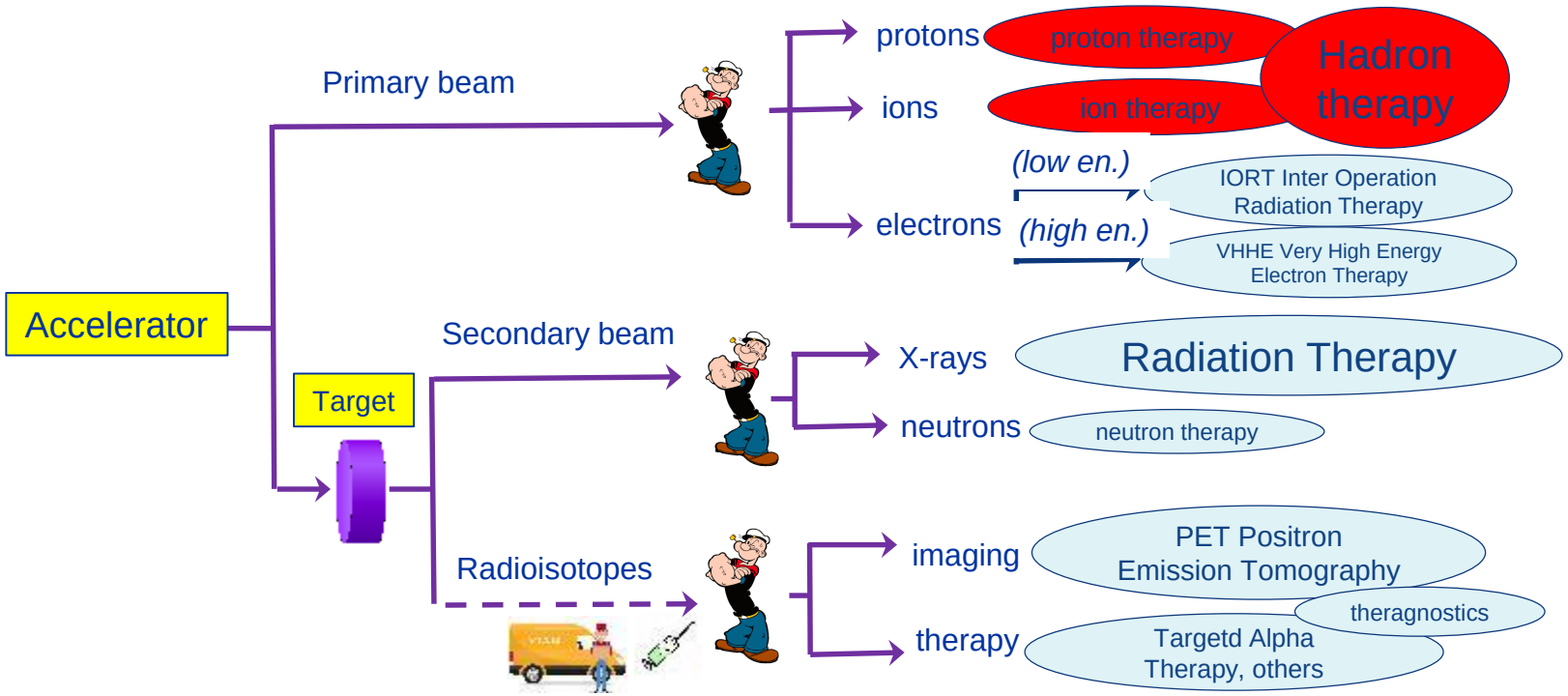
STELLA

Smart **T**echnologies to **E**xtend **L**ives with **L**inear **A**ccelerators

Country	LINACs	Population	People per LINAC
Ethiopia	1	115 M	115,000,000
Nigeria	7	206 M	29,000,000
Tanzania	5	59.7 M	11,900,000
Kenya	11	53.9 M	4,890,000
Morocco	42	36.9 M	880,000
South Africa	97	59 M	608,000
UK	348	67 M	195,000
Switzerland	72	86 M	119,000
US	3827	331 M	87,000

- **29** countries have LINAC-RT facilities
- **12** countries only one facility
- **26** no LINACs for RT
- **~400** RT-LINACs for > **1.2 billion** people

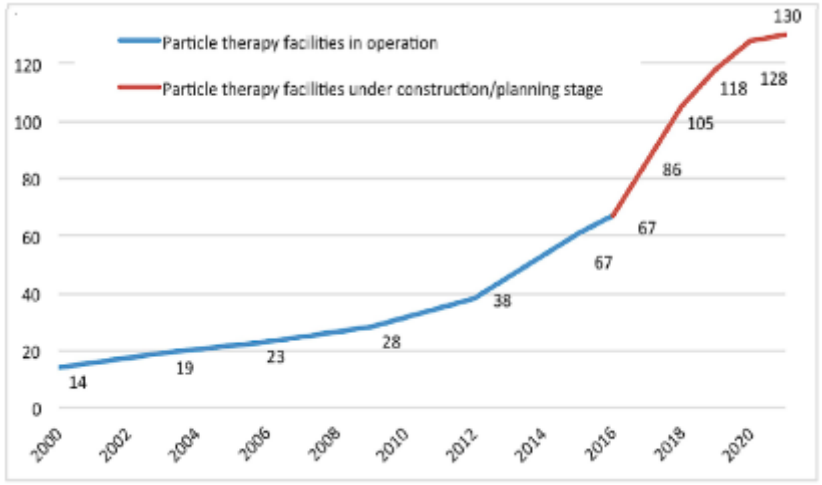
2 – Hadron therapy



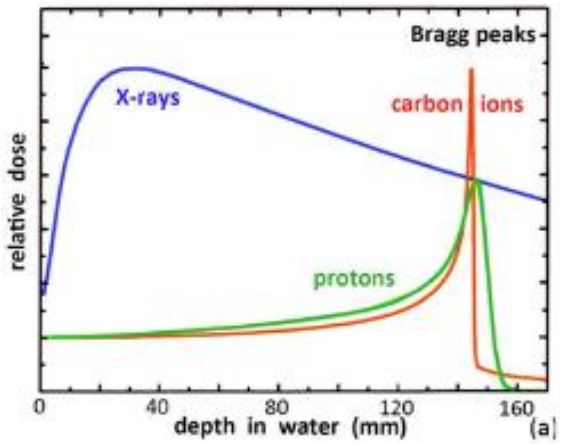
Treating cancer with particle beams

Cancer today: ~ 65% of cancers are curable; ~ 35% of cancer treatments fail, 2/3 because of metastasis, 1/3 in the primary site.

- **Priority of cancer research** is treating the >10% “not curable” cancers, usually large, deep seated, radioresistant.
- **Techniques**: Advanced Radiation Therapy (e.g. IMRT), or **Hadron Therapy** (protons or ions).
- **Challenge**: Deposit enough dose on the cancer, sparing the surrounding tissues (secondary cancers, quality of life).



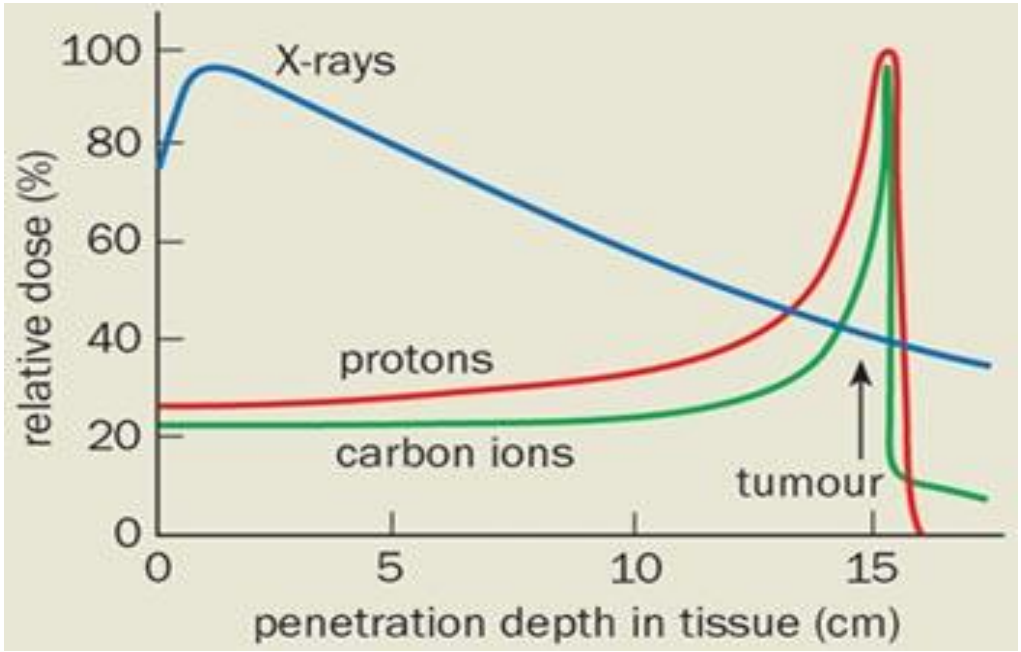
Hadron Therapy (or **Particle Therapy**) allows concentrating the radiation dose on the tumour, thanks to the «Bragg peak».
More **expensive** than X-ray therapy, is rapidly growing thanks to new compact industry-made proton accelerators.



The Bragg peak

Bethe-Bloch equation of ionisation energy loss by charged particles

$$-\frac{dE}{dx} = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I.(1-\beta^2)}\right) - \beta^2\right]$$



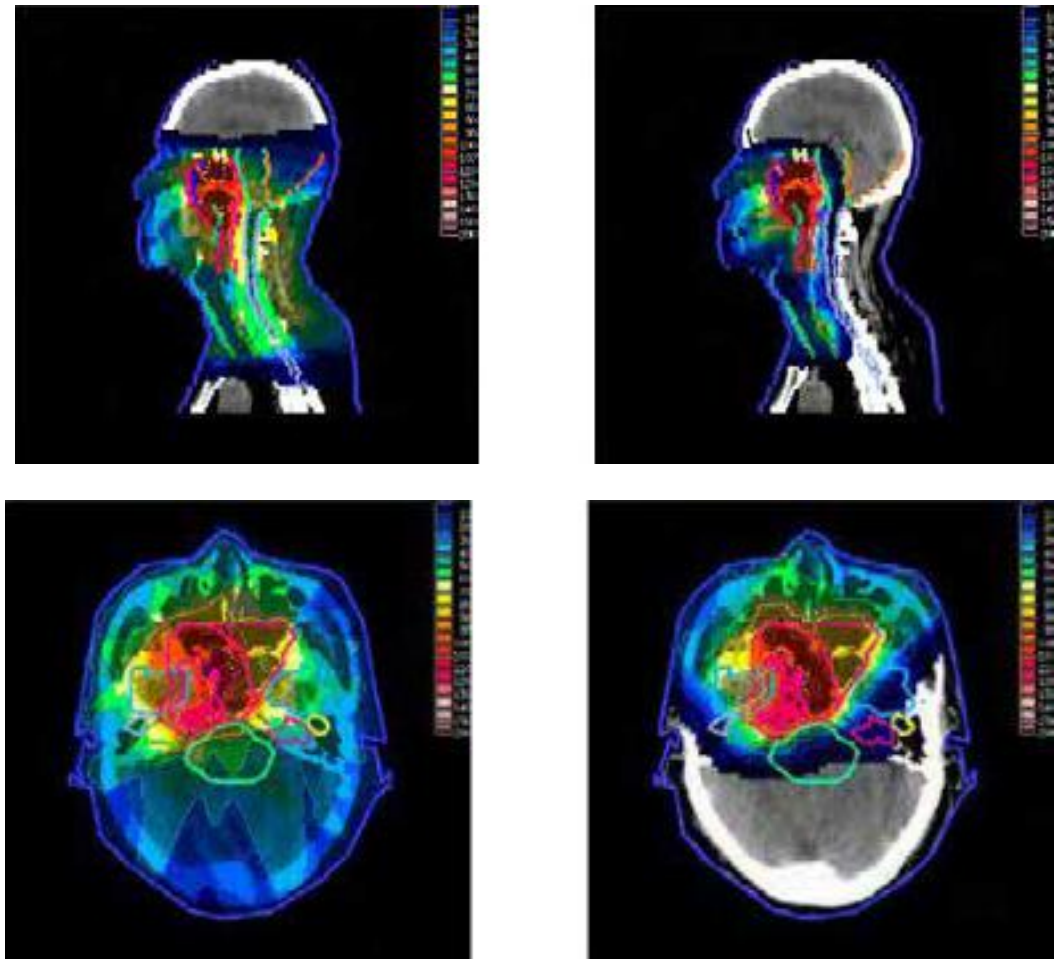
«Bragg» peak

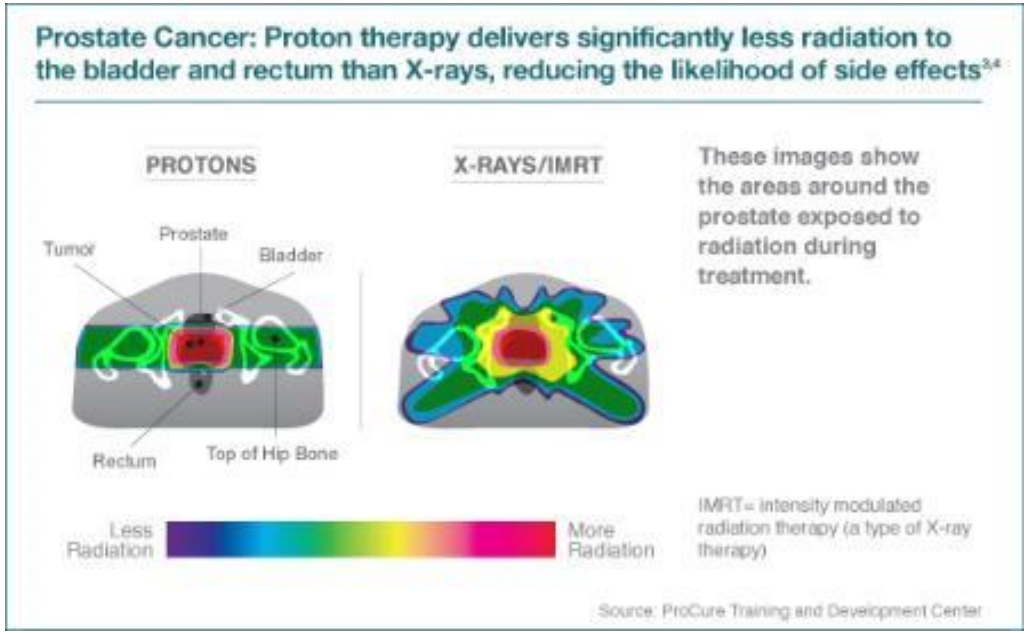
Different from X-rays or electrons, protons and ions deposit their energy at a given depth inside the tissues, **minimising the dose to the organs close to the tumour**.

Required energy (protons) about 230 MeV, corresponding to 33 cm in water.
Small currents: 10 nA for a typical dose of 1 Gy to 1 liter in 1 minute.

accelerators-for-society.org

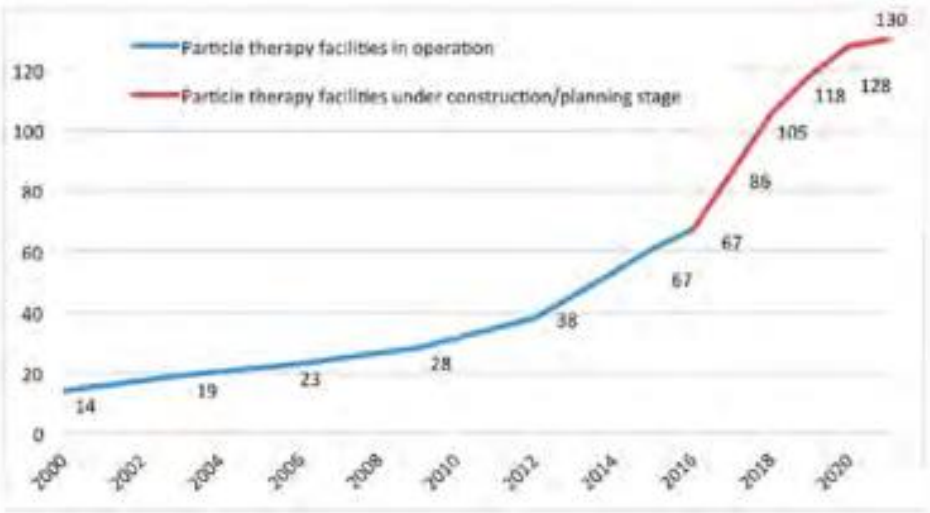
Comparing proton and X-ray therapy





The results of irradiating a nasopharyngeal carcinoma by X-ray therapy (left) and proton therapy (right), showing the potential reduction in dose outside the tumour volume that is possible with proton treatment. (Z. Taheri-Kadkhoda et al., Rad. Onc., 2008, 3:4 – from APAE Report, 2017).

The rise of particle therapy



First experimental treatment in 1954 at Berkeley.

First hospital-based proton treatment facility in 1993 (Loma Linda, US).

First treatment facility with carbon ions in 1994 (HIMAC, Japan).

Treatments in Europe at physics facilities from end of ‘90s.

First dedicated European facility for proton-carbon ions in 2009 (Heidelberg).

From 2006, commercial proton therapy cyclotrons appear on the market (but Siemens gets out of proton/carbon synchrotrons market in 2011).

Nowadays 3 competing vendors for cyclotrons, one for synchrotrons (all protons).

More centres are planned in the near future.

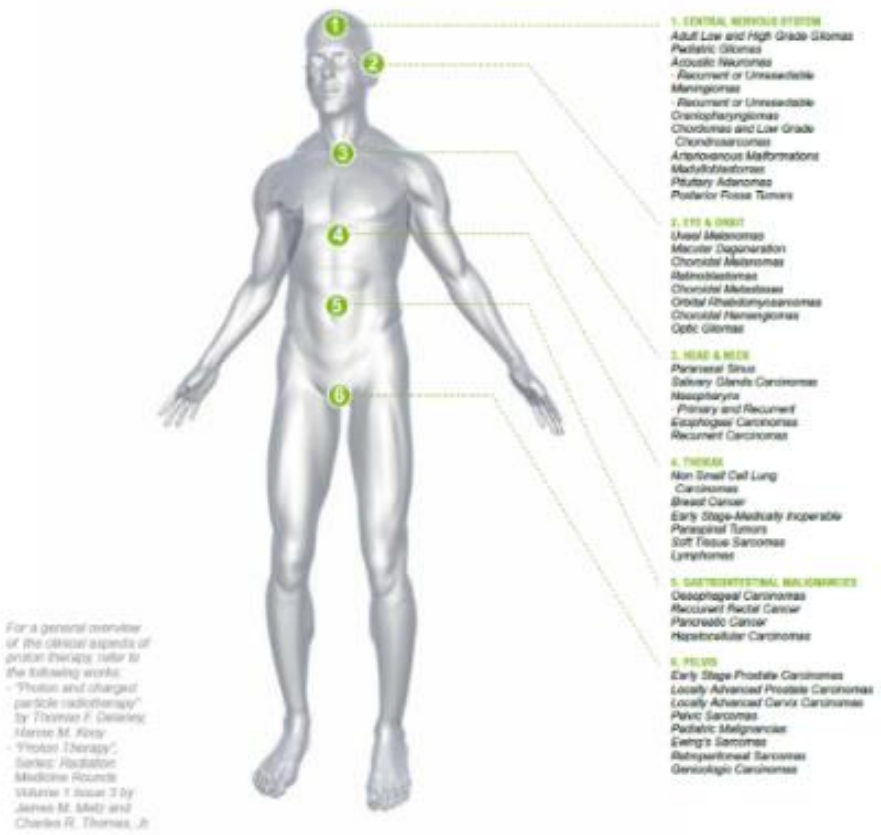
A success story, but …

many ongoing discussion on effectivness, cost and benefits.

The difficulties of particle therapy

- **Cost**: a commercial single-room proton therapy system has a price starting from 30 M€, to be compared with 2-3 M€ of a X-ray radiotherapy system. A complex proton and ion therapy centre has a cost of 150-200 M€.
- **Effectiveness**: there is no or little evidence for a different effectiveness between protons and X-rays. They have the same radiobiological effect and when the same dose is applied, the effect is the same.
- **Quality of life**: protons and ions are superior in sparing the surrounding tissues thus reducing risk of secondary cancer and improving quality of life after treatment. But while survival rates are easy to measure and compare, quality of life is not an easily measureable parameter. Only recently studies have been started, but will take years.
- **Optimisation**: the effect of protons and ions is not as known as that of X-rays, and optimisation of treatment is still ongoing. Biological tests are needed to compare the loss of energy (Bragg peak) to the effect on the cells – not necessarily linear.
- **Centralisation of medicine**: the high cost of particle treatment calls for large centralised units that have difficulties in attracting patients from other hospitals.

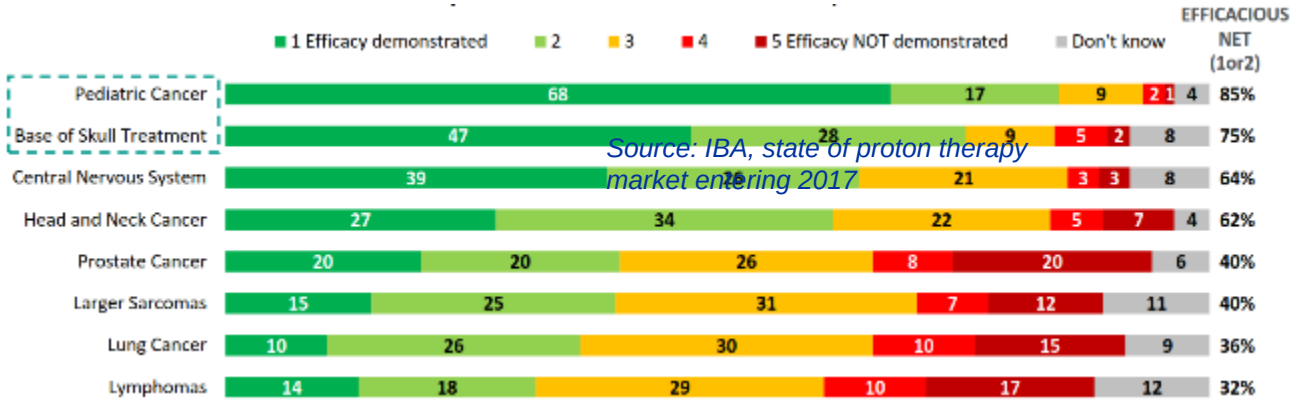
Advantages of proton therapy



Source: IBA proton therapy fact-sheet,

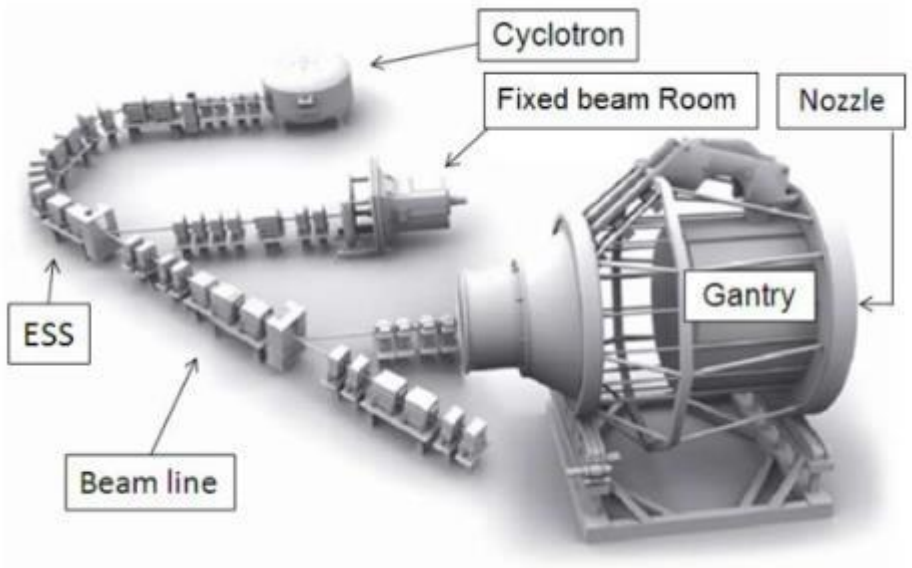
The main recognised advantage of proton therapy are for:

- **Pediatric tumours**, where surrounding tissues are more delicate and the risk of secondary tumours is higher.
- **Tumours close to vital organs**: base of skull, central nervous system, head and neck.



Source: IBA, state of proton therapy market entering 2017

Proton therapy accelerators: cyclotrons



At present, the cyclotron is the best accelerator to provide proton therapy reliably and at low cost (4 vendors on the market).

Critical issues with cyclotrons:

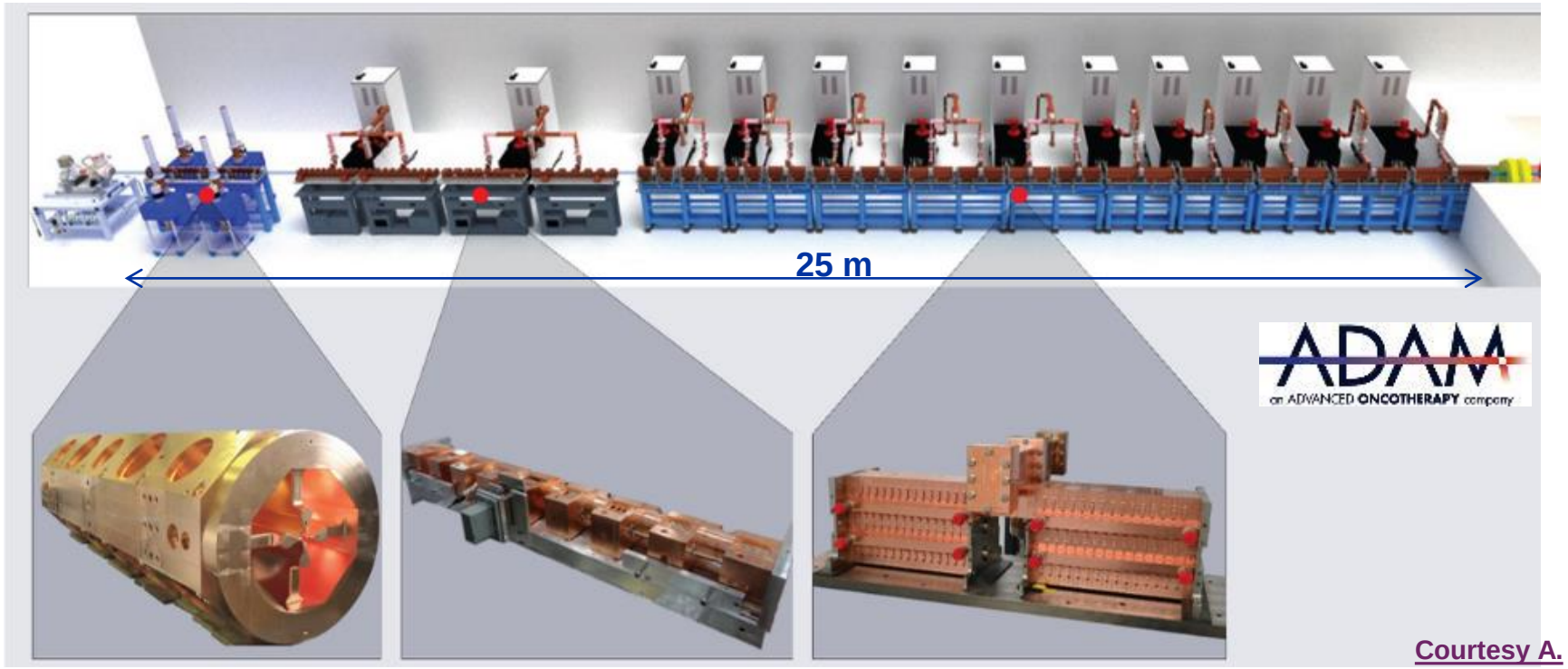
1. Energy modulation (required to adjust the depth and scan the tumour) is obtained with degraders (sliding plates) that are slow and remain activated.
2. Large shielding

ProteusOne and ProteusPlus turn-key proton therapy solutions from IBA (Belgium)

A linac alternative: LIGHT (Linac for Image Guided Hadron Therapy)

The LIBO prototype structure and accelerating cells (CERN)

Advantages of a LINAC:
- High repetition frequency with pulse-to-pulse energy variability
- Small emittance, no beam loss.



Courtesy A. Degiovanni,

750 MHz Radio Frequency Quadrupole (RFQ)

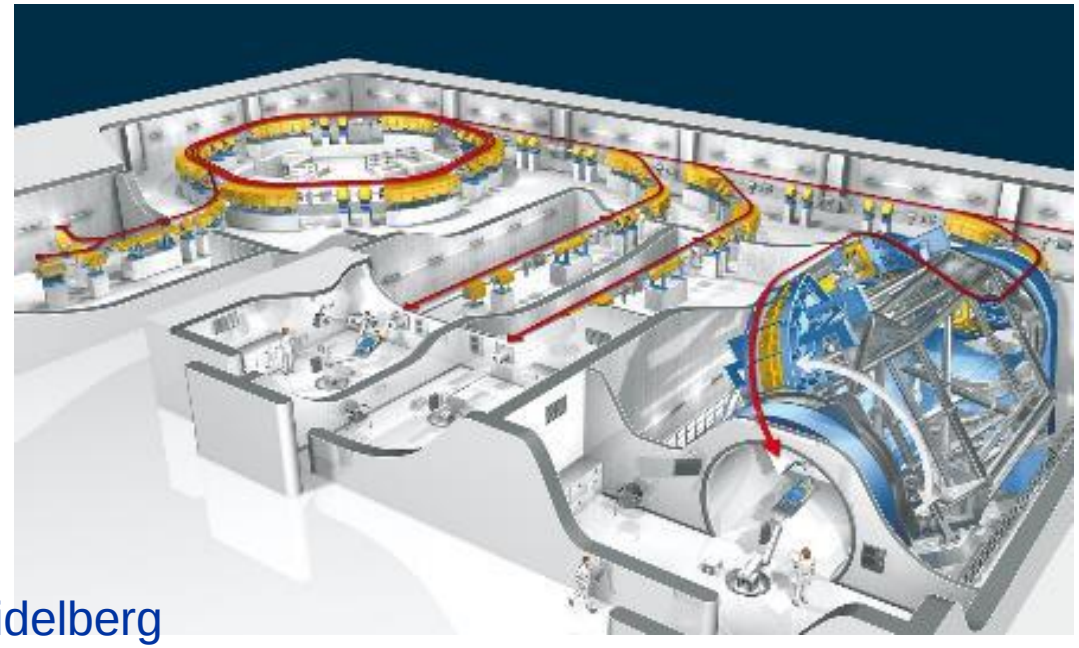
3 GHz Side Coupled Drift Tube Linac (SCDTL)

3 GHz Coupled Cavity Linac (CCL)

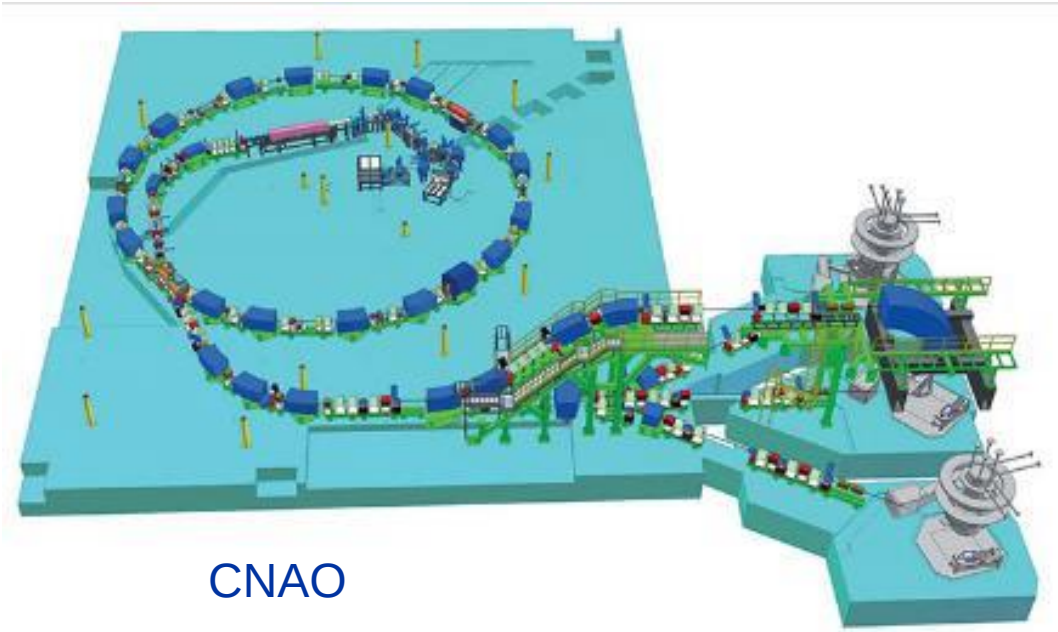
ADAM is an old CERN spin-off now part of the UK company AVO (Advanced Oncotherapy). They reported acceleration to 52 MeV in September 2018. From end 2019, the development will continue at Daresbury Laboratory (UK). The first LIGHT unit will be installed at the Harley Street Hospital in London.

Synchrotrons for proton and ion therapy

- The Loma Linda Medical Centre in US (only protons) and the ion therapy centres in Japan have paved the way for the use of synchrotrons for combined proton and ion (carbon) therapy).
- 2 pioneering initiatives in Europe (ion therapy at GSI and the Proton-Ion Medical Machine Study PIMMS at CERN) have established the basis for the construction of 4 proton-ion therapy centres: Heidelberg and Marburg Ion Therapy (HIT and MIT) based on the GSI design, Centro Nazionale di Terapia Oncologica (CNAO) and Med-AUSTRON based on the PIMMS design.

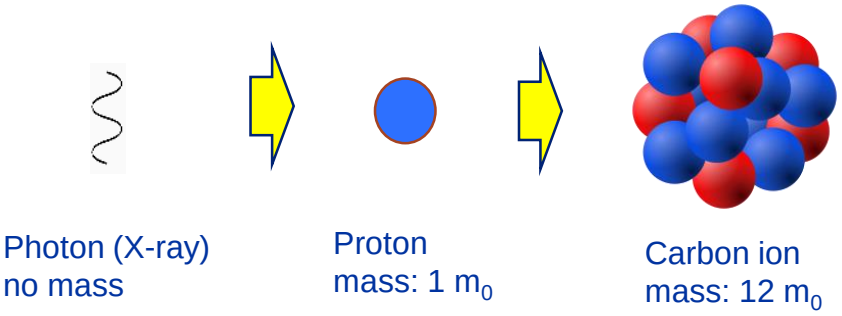


HIT Heidelberg



CNAO

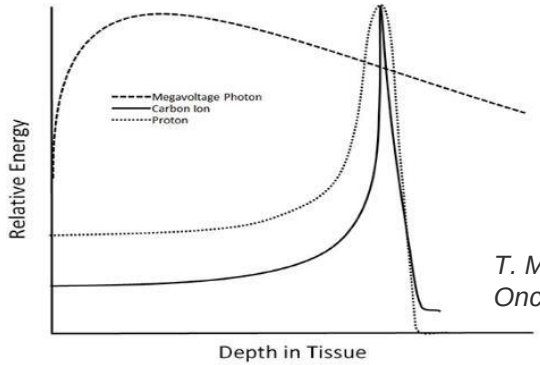
Ion therapy: from photons to protons to ions



Photon (X-ray)
no mass

Proton
mass: 1 m_0

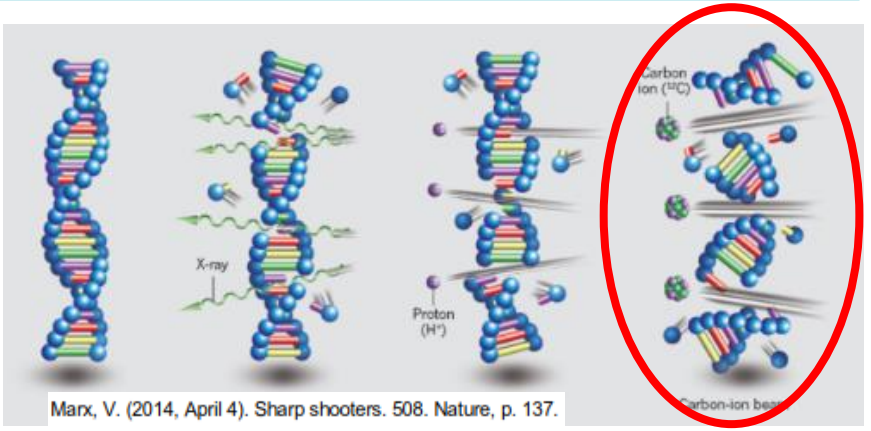
Carbon ion
mass: 12 m_0



T. Malouff, Front. Oncol., 04.02.2020

Advantages of cancer therapy with ions heavier than protons:

- **Higher energy deposition** and ionisation per length generates non-reparable double-strand DNA breakings.
- Energy deposition more precise, with lower straggling and scattering
- Effective on hypoxic radioresistant tumours.
- Opportunities from combination with immunotherapy to treat diffused cancers and metastasis.



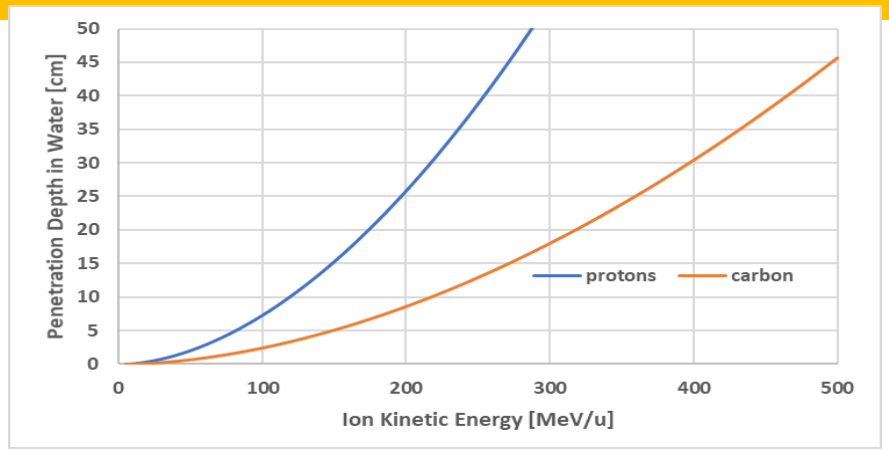
Marx, V. (2014, April 4). Sharp shooters. 508. Nature, p. 137.

- Only carbon ions licensed for treatment (for historical and practical reasons)
- First patient treatments with carbon ions only in 1994: ion therapy is still in its infancy !

Ion therapy: accelerator challenges

Particle accelerators for heavy ions are large and complex:

1. The high energy deposition means that to reach deep seated tumours ions must be accelerated to **higher energies** than protons: ion energy loss goes as (charge of the incident particle)^2. → around 440 MeV/u for carbon, compared to 240 MeV for protons.



$$B\mathrm{r}\,[T.m] = 3.3356 \times pc[GeV]$$

Magnetic rigidity Bρ for carbon ions at full energy is **2.76 times higher** than protons.

→ **For cyclotrons and synchrotrons, accelerator diameter scales with rigidity**

2. The required energies fall into a **transition range between accelerator technologies**: cyclotrons and linacs are better at low energies, synchrotrons at high energies. In the intermediate region, there is not an **ideal accelerator** configuration → need to compare options, characterised by **complexity, cost, and R&D requirements**.

For a given magnet field, in an ion synchrotron or cyclotron accelerator and gantry are almost 3 times larger than for protons. The HIT gantry has a mass of 600 tons for a dipole bending radius of 3.65 m.

Required treatment energies for different ions

Properties ions in warm synchrotrons designed for protons, 3He2+, 4He2+ and 12C6+:

particle	energy [MeV/u]	rigidity [Tm]	range [cm]	synch circumf [m]	comment	proton energy [MeV]	remarks
p	230	2.33	33.6	23	proton in proton machine	230	
3He2+	109	2.33	6.45	23	3He2+ in proton machine	230	
--	270	3.82	33.6	38	3He2+ in 3He2+ machine	540	
4He2+	64	2.33	3.25	23	4He2+ in proton machine	230	
--	162	3.82	17.6	38	4He2+ in 3He2+ machine	540	4He2+ range 18 cm
--	230	4.63	33.4	46	4He2+ in 4He2+ machine	730	12C6+: 11.1 cm
12C6+	64	2.34	1.08	23	C in proton machine	230	
--	162	3.82	5.8	38	C in 3He2+ machine	540	
--	230	4.63	11.1	46	C in 4He2+ machine	730	
--	421	6.54	33.4	65	C in C machine	1250	

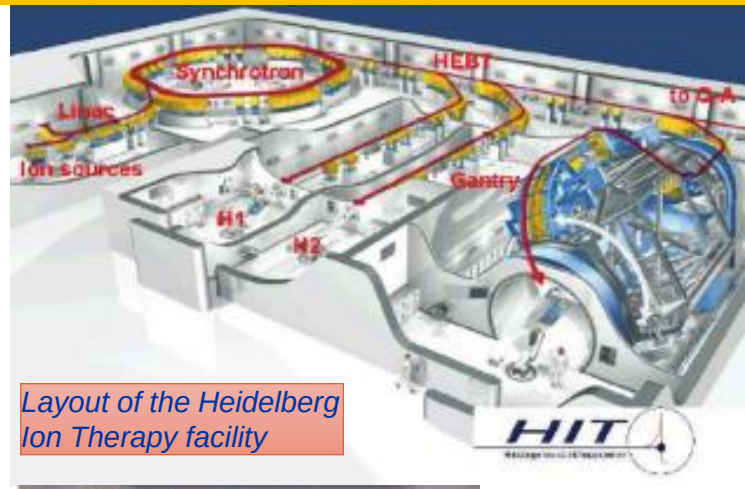
Intensity needed to irradiate 1 dm3 tumor with 2 Gy:

- 12C6+: 1e10, ion source current: ~ 500 uA C4+
- 4He2+: 4.5e10, ion source current: ~ 1125 uA
- 3He2+: 5e10, ion surce current: ~ 1250 uA

Table courtesy of Mariusz Sapinski (CERN and SEEIIST, presently PSI)

Present and the future of ion therapy accelerators

The main limitation to the diffusion of ion therapy is the cost and size of the accelerator



Layout of the Heidelberg Ion Therapy facility

Only 4 ion therapy facilities operating in Europe (+ 6 in Japan, 3 in China, 1 in construction in US)

- CNAO and MedAustron based on a design started at CERN in 1996. 1st patient: CNAO, 2011.
- HIT and MIT based on a design started at GSI (Germany) in 1998 . 1st patient: HIT, 2009.

- The present generation of ion facilities is based on large accelerator designs of the 90's, derived from scientific accelerators.
- In the meantime, proton therapy has already moved to a new generation of compact industry-made accelerators.
- Particle accelerator technology has made a huge progress in the last 20 years, and it is time now to explore new accelerator designs for ion therapy that may profit of the latest advances in accelerator technologies.

New developments in particle therapy

- **Pencil Beam Scanning (PBS)**: (or Intensity-Modulated Particle Therapy IMPT) scanning through the tumour of a small pencil beam, to reduce even more the dose to surrounding organs.
- **Motion Management**: following the movements of the patients (breathing, etc.) with the movement of the beam. It is often called 4-D scanning.
- **Adaptive image guided therapy (IGPT)**: combining proton therapy and MRI.
- **Imaging from secondary emission**: imaging during treatment is possible by monitoring secondary emission from the particle beam.
- **Use of other ions**: intermediate ions like e.g. Helium seem to have similar properties than Carbon, while being easier to accelerate. Oxygen and Argon are also considered. More clinical studies and accelerator design effort are needed.
- **Particle beams for other diseases than cancer:** interest for cardiac arrhythmia and other applications.
- **Compact gantries:** the gantry is a critical element of particle therapy centres, in terms of cost, dimensions and limitation to scanning speed. Options being considered are superconducting magnets, FFAG, full accelerators on gantries, etc.

New trends: FLASH irradiation

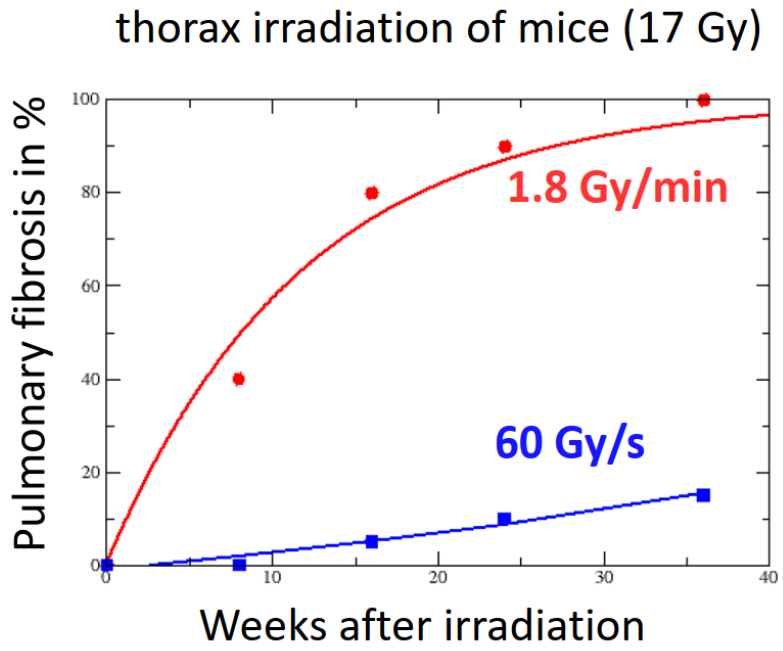
Treating tumours delivering radiation in short pulses at ultra-high dose rates, to spare healthy tissues around the tumour.
Dose delivered in **fractions of a second instead of several minutes**.

First observed in the 70's, rediscovered in 2014 (Favaudon and Vozenin), 1st treatments 2014-18, 1st clinical trial in 2020.

Several theories to explain the experimental data, all somehow related to Oxygen depletion and time to restore Oxygen in cells.

Does not work with photons (X-rays)
Being tested worldwide with electrons and protons
To be tested with carbon ions

Challenges:
- Dosimetry
- Deep tumours, large volumes

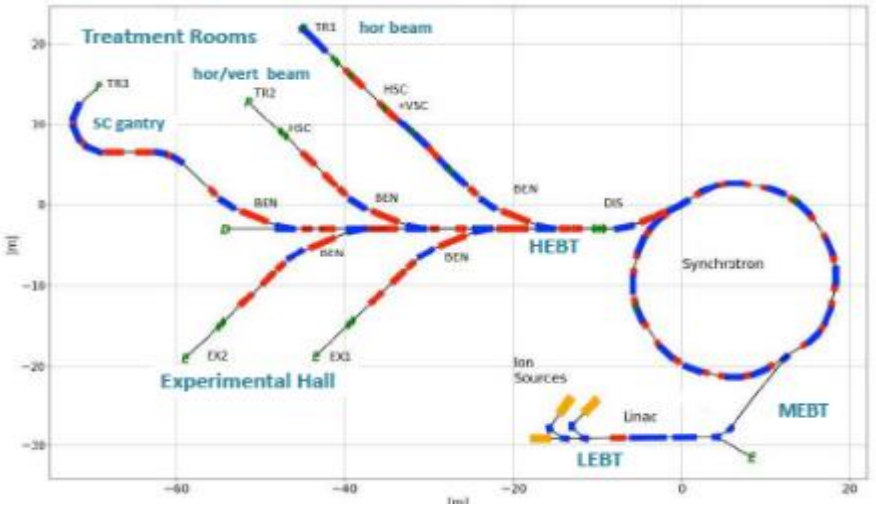


Favaudon et al., Sci Transl Med 6 (2014) 245ra93
DOI: 10.1126/scitranslmed.3008973

Conventional synchrotron

Ongoing improvements to PIMMS design developed at CERN in 1995/2000

- Higher beam intensity for faster treatment ($2x10^{10}$, 20 times higher than CNAO or HIT)
- Multiple energy extraction (**multiple flat-tops**)
- Additional **fast extraction for FLASH operation**
- Redesigned **linac** at higher frequency, for lower cost and parallel isotope production
- Multiple particles: p, He, C, O
- Optimised layout of beam transport, for both research and therapy



Optimised layout recently developed for the SEEIIST initiative

Room temperature magnets at 1.6 T field

Injection/Acceleration	Unit					
Particle after stripping		**p**	**$^{4}He^{2+}$**	**$^{12}C^{6+}$**	**$^{16}O^{8+}$**	**$^{36}Ar^{16+}$**
Energy	MeV/u	7				
Magnetic rigidity at injection	Tm	0.38	0.76	0.76	0.76	0.86
Extraction energy range (**)	MeV/u	60 – 250 (1000)	60 – 250 (430)	100 - 430	100 - 430	200 – 350
Magnetic rigidity at highest energy (for therapy)	Tm	2.42	4.85	6.62	6.62	6.62
Maximum nominal field	T	1.5				
Maximum number of particles per cycle		$2.6 \cdot 10^{11}$	$8.2 \cdot 10^{10}$	$2 \cdot 10^{10}$	$1.4 \cdot 10^{10}$	$5 \cdot 10^{9}$
Ramp-up rate	Tm/s	<10				
Ramp-down time of magnets	s	1				
Spill ripple, intensity ratio I_{max}/I_{mean} (average on 1 ms)		< 1.5				
Slow extraction spill duration with multi-energy	s	0.1 – 60				
Fast extraction	s	$< 0.3\ 10^{-6}$				

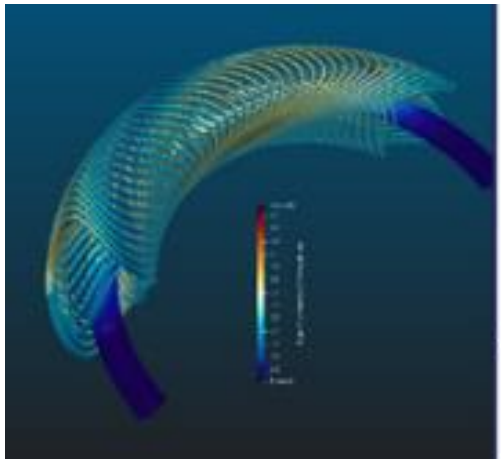
Development of superconducting magnets for ion therapy

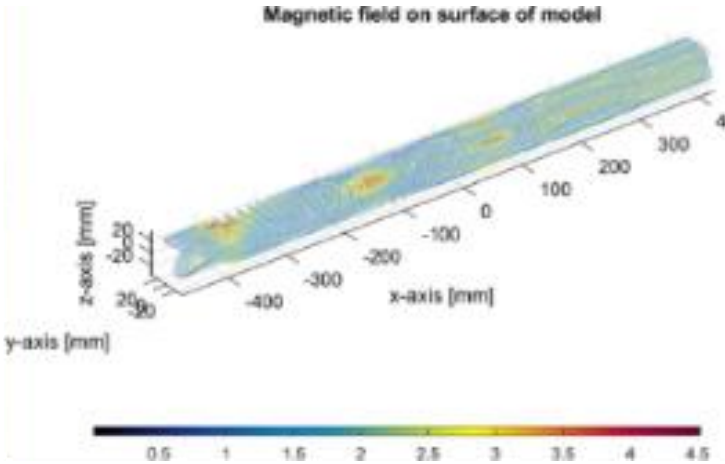
Wide international effort towards the development of a new generation of superconducting magnets for small synchrotrons.

Some of the challenges are common with magnets for scientific applications, other specific for medical accelerator magnets: ramping field, curved shape, quadrupole integration, use of cryocoolers.

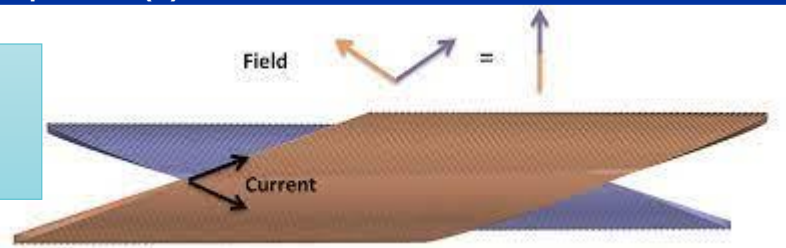
Magnet Parameters

Parameter	Synchrotron magnet	Prototype Magnet
Bρ (Tm)	6.6	6.6
B_0 dipole (T)	3.0	4-5
Coil apert. (mm)	70-90	60 (90)
Curvature radius (m)	2.2	2.2 , ∞
Ramp Rate (T/s)	1	0.15-1
Field Quality (10^{-4})	1-2	10-20
Deflecting angle	90°	0 - 45°
Alternating-Gradient	yes (triplet)	N/A
Quad gradient (T/m)	40	40
B_{quad} peak (T)	1.54- 1.98	1.2
B_{peak} coil (T)	4.6 - 5	5.6-7
Operating current (kA)	< 6	< 5
Type of Superconductor	NbTi (Nb_3Sn)	NbTi (curved), HTS (straight)
Operating temperature (K)	5 (8)	5 (20)



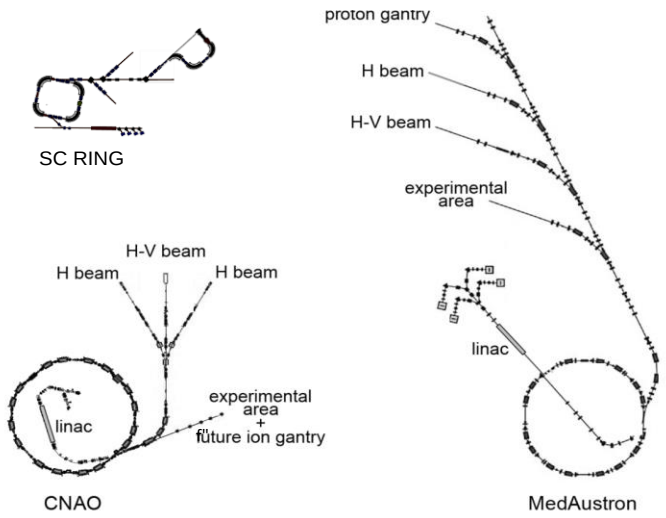


Canted Cosine Theta magnets
(drawing: E. Oponowicz)



Solution for curved and straight CCT coils combining dipole and quadrupole in the same winding - Courtesy G. Kirby and J. van Nugteren, CERN

Superconducting synchrotron



A superconducting C-ring at the same scale of CNAO and MedAustron

Advantages:

- Smaller dimensions
- Lower construction and operation cost
- Reduced power consumption

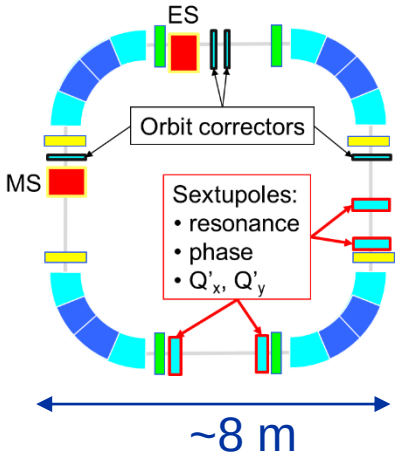
Need: 3 – 5 T magnets ramped at 1 T/s

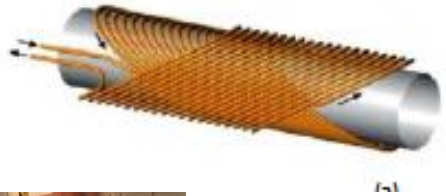
Circumference	27 m
Injection energy	7 MeV/u
Extraction energy	100 → 430 MeV/u
Straight section 1	3 m
Straight section 2	3.6 m
AG-CCT Max. bending field	3.5 T
AG-CCT Bending radius	1.89 m
AG-CCT Magnetic bending angle	90°

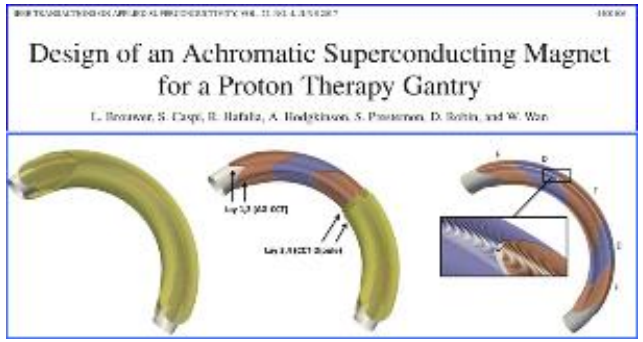
Magnet options to be explored:

- Conventional Nb-Ti
- Canted Cosine Theta
- High Temperature Superconductivity

CCT magnets 3.5T
Aperture 60 mm
Total circumference 27 m





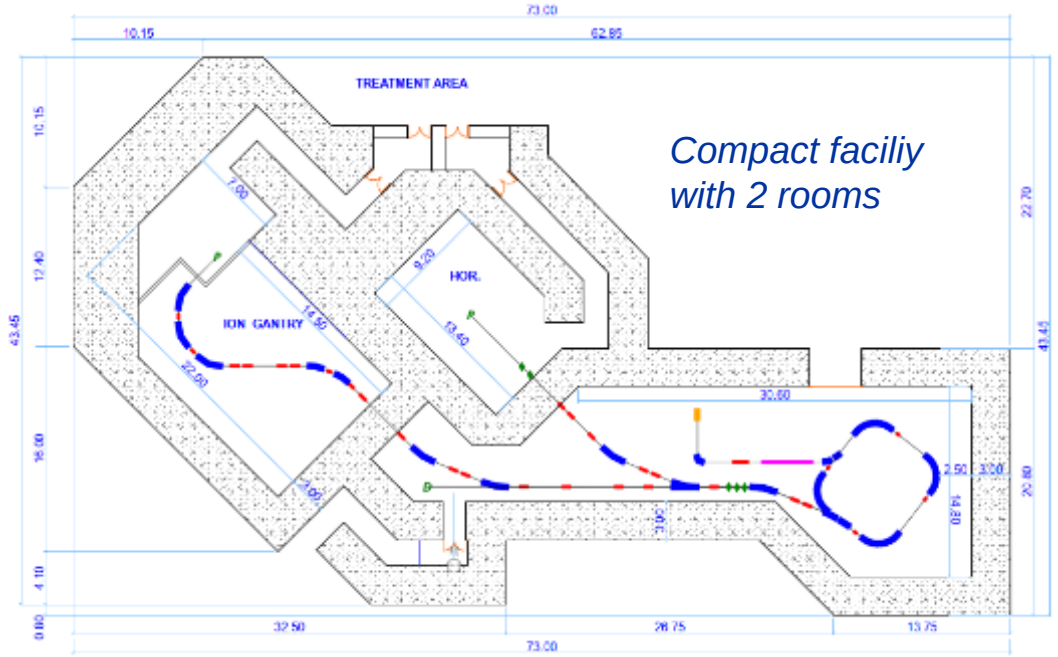


Canted Cosine Theta magnets

Proposed by TERA, based on the LBNL experience in the design and prototyping of a proton gantry magnet
Layered construction, can include quadrupole layers

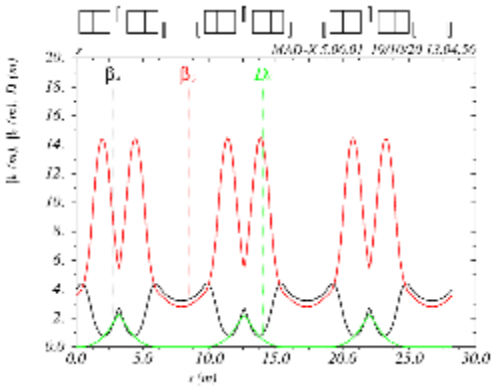
The compact SC synchrotron

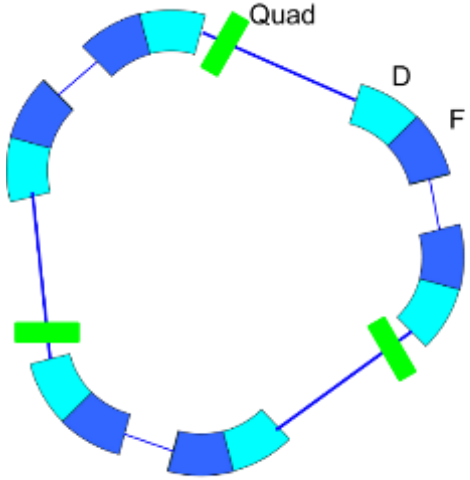
E. Benedetto, M. Sapinski, TERA/SEEIIST
P. Foka, GSI
D. Kaprinis, Kaprinis Architects
M. Vretenar, CERN



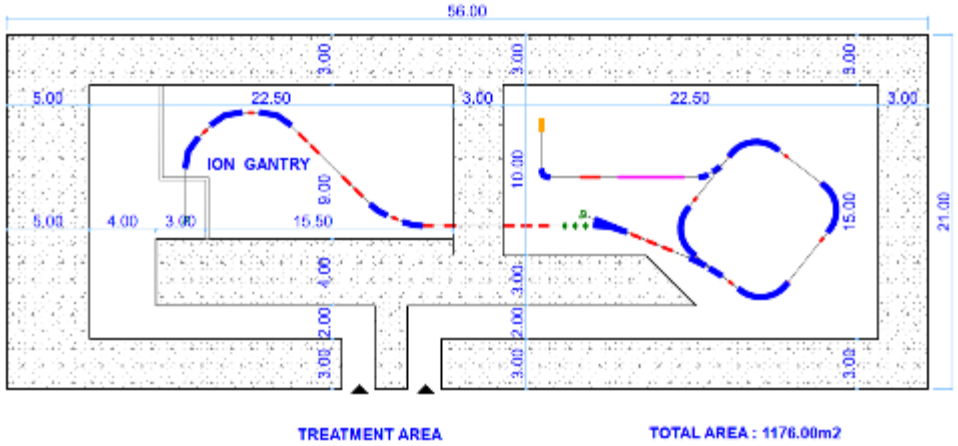
Compact faciliy with 2 rooms

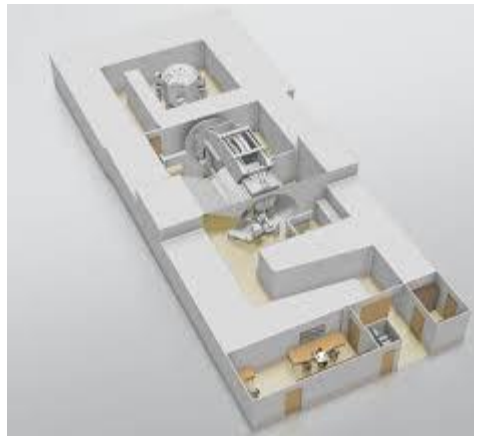
Alternative lattice with 60⁰ magnets





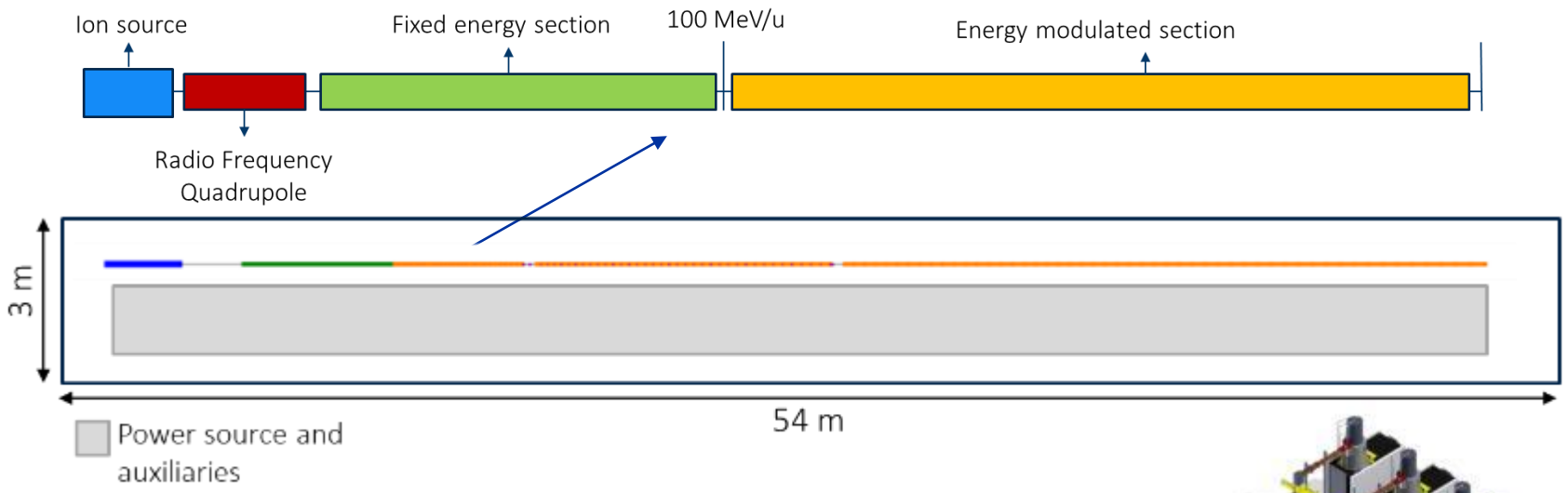
A compact single-room ion therapy facility in about 1,000 m²





Comparable in size with proton therapy systems – here the single-room proton facility ProteusOne, from IBA)

Carbon linac



Fully stripped C, can accelerate p, He

Based on an original idea by U. Amaldi (CABOTO)

3 GHz accelerator, 750 MHz injector

High-energy part similar to LIGHT p-linac of ADAM/AVO, fixed energy section to be developed.

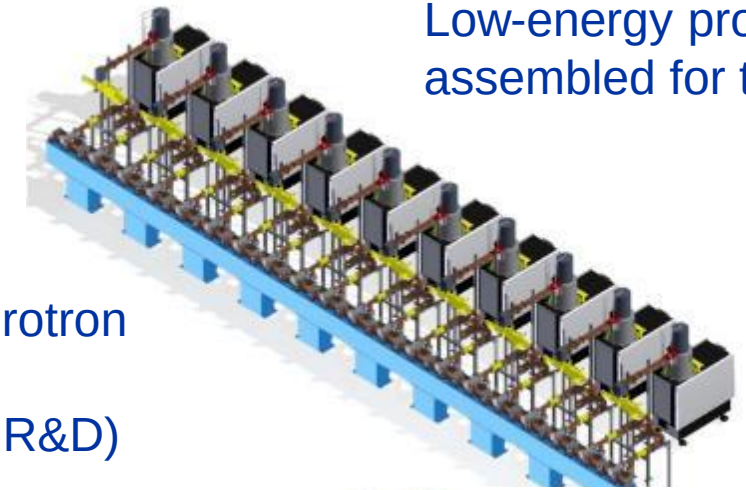
Low-energy prototype section being assembled for testing at CERN

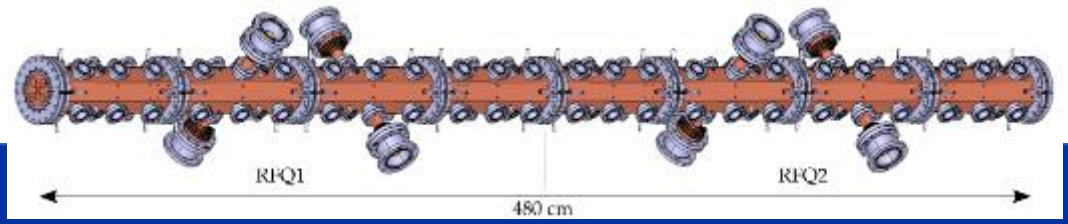
Advantages:

- Modular (can be built in stages)
- Fast energy variation (longitudinal scan of tumour)
- Smaller and less expensive than standard carbon synchrotron

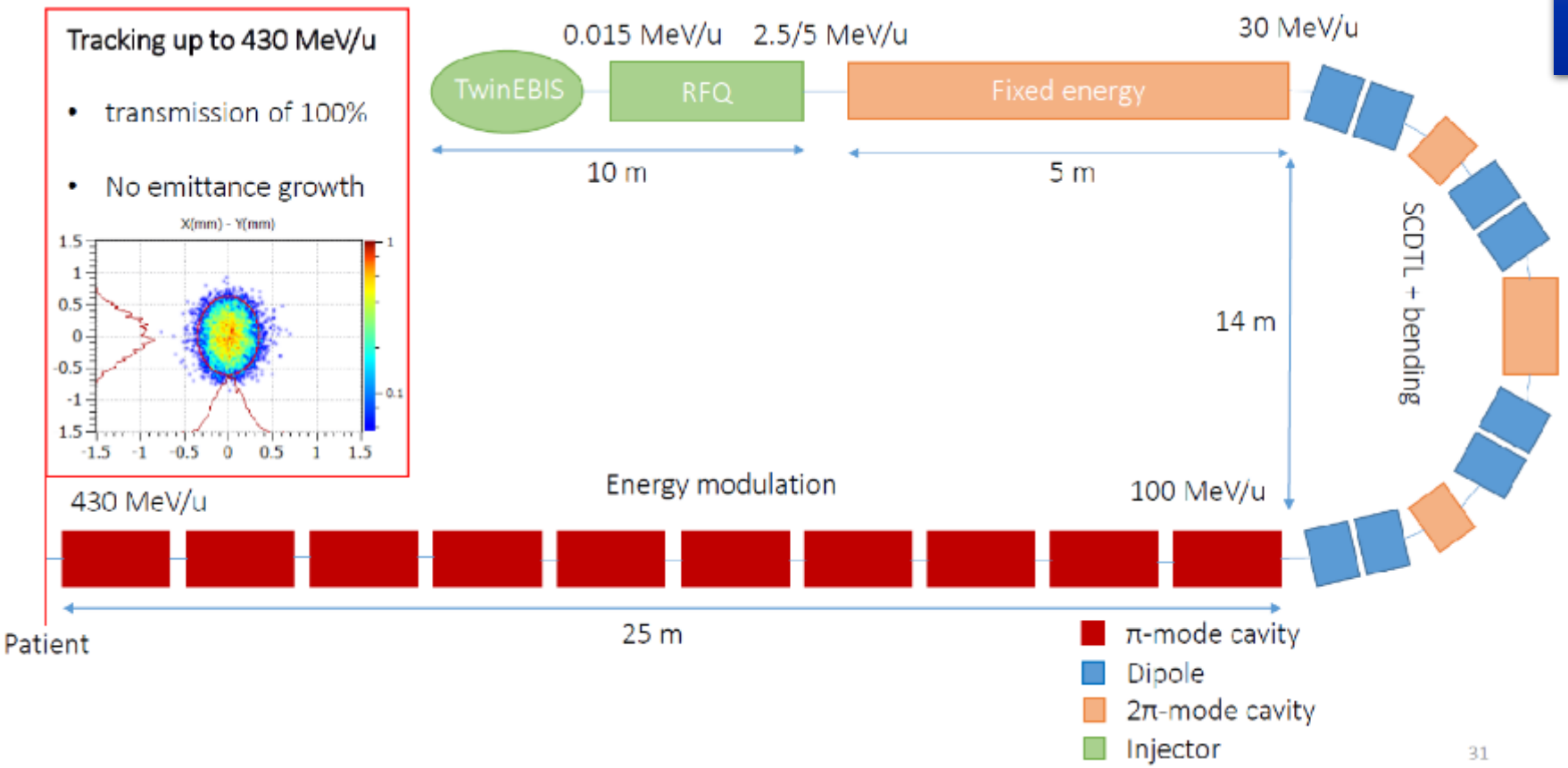
Disadvantages:

- No design of intermediate energy cavities exists (needs R&D)
- No gantry design exists (with large energy acceptance)





Carbon linac – bent version



High repetition frequency (360 Hz) with pulse-to-pulse energy modulation allow fast and accurate dose delivery to the tumour

Parameter	Value
Frequency	750 MHz/3 GHz
Species	$^{12}C^{6+}$
Final energy	100-430 MeV/u
Repetition rate	200 (400) Hz
Pulse length	5 µs

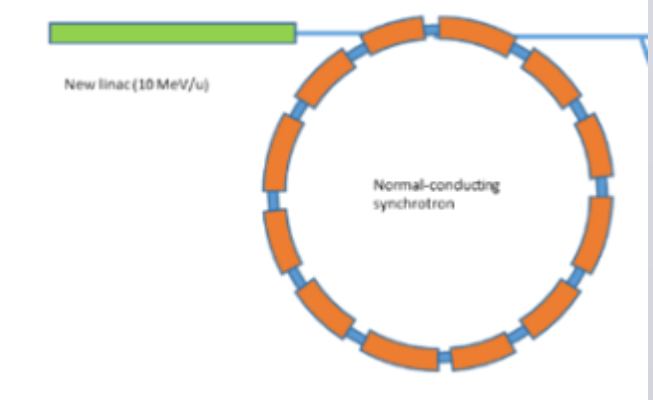
Beam dynamics design completed at CERN

Advanced ion therapy: 3 alternative accelerator designs

Improved synchrotron (warm)

Equipped with several innovative features: multi-turn injection for higher beam intensity, new injector at higher gradient and energy, multiple extraction schemes, multi-ion.

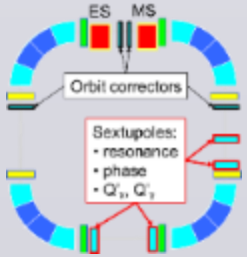
Circumference ~ 75 m

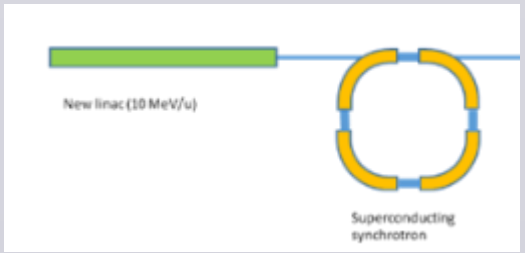


Improved synchrotron (superconducting)

Equipped with the same innovative features as warm, but additionally 90^0 superconducting magnets.

Circumference ~ 27 m

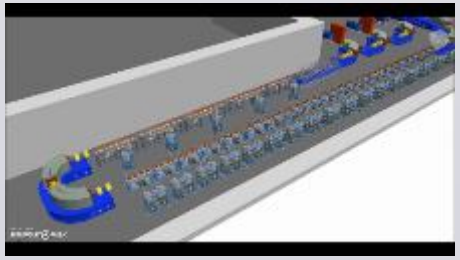


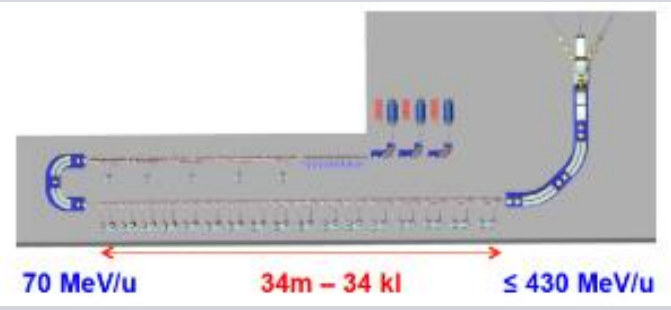


Linear accelerator

Linear sequence of accelerating cells, high pulse frequency.

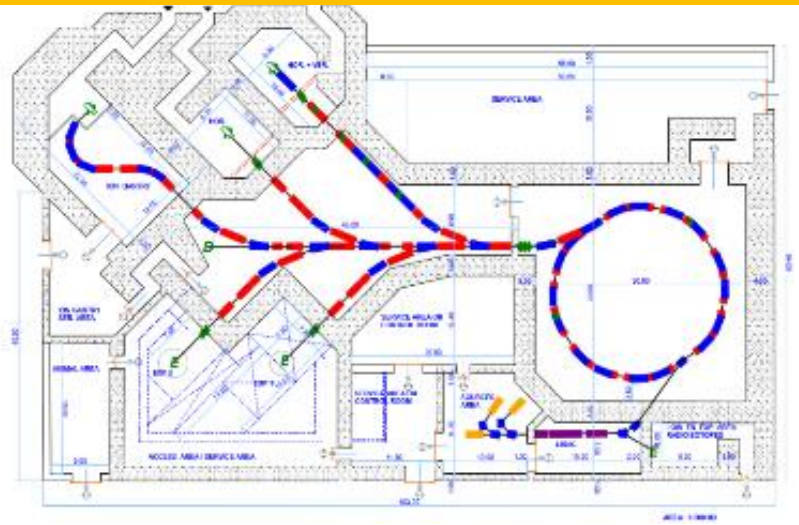
Length ~ 53 m



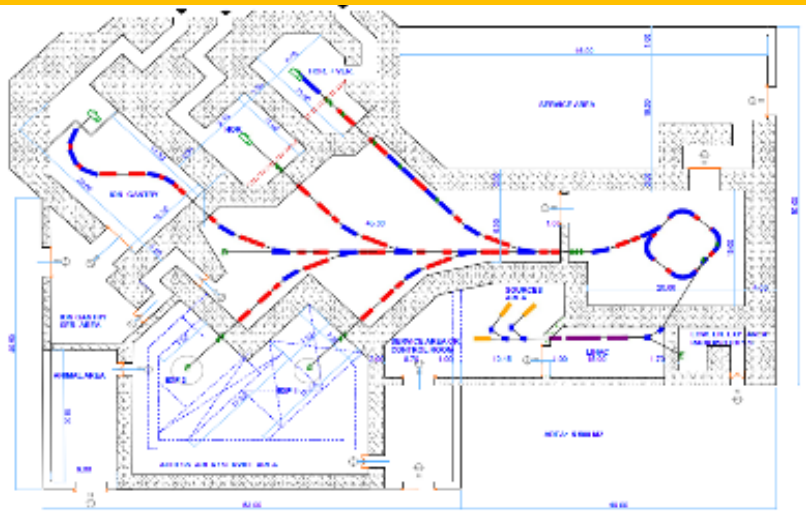


Other options considered as less interesting because of cost and/or required R&D: **RC synchrotron**, **FFAG**, **SC cyclotron**, **PWFA**

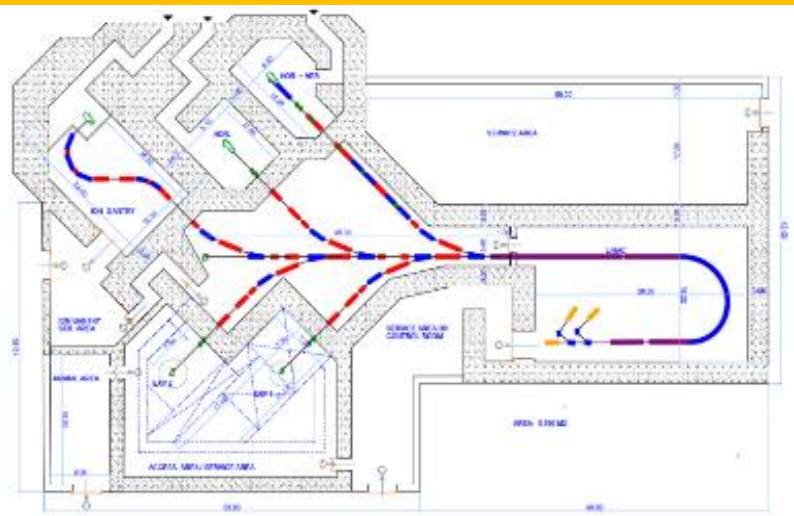
Comparing three accelerator options for SEEIIST



RT synchrotron:
accelerator 1,200 m^2, facility 6,500 m^2
Reference for cost calculation



SC synchrotron:
accelerator 600 m^2, facility 5,500 m^2
estimated cost (acc. only): 20% lower



Full linac:
accelerator 600 m^2, facility 5,500 m^2
estimated cost (acc. only): 20% lower

SC synchrotron or linac allow 50% reduction in accelerator dimensions, 15% in overall facility dimensions, and 20% reduction in cost.

- The **SEEIIST** (South East Europe International Institute for Sustainable Technologies) is a new international partnership aiming at the construction of a new Research Infrastructure for cancer research and therapy in South East Europe (9 member countries).
- Supported by the European Commission, to develop the facility design in collaboration with CERN.

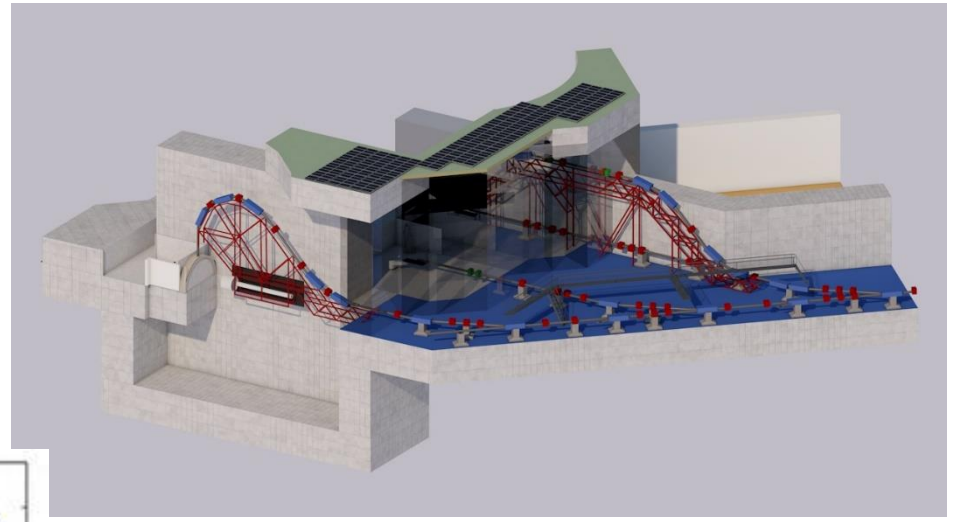
SEE IIST
South East European International Institute for Sustainable Technologies

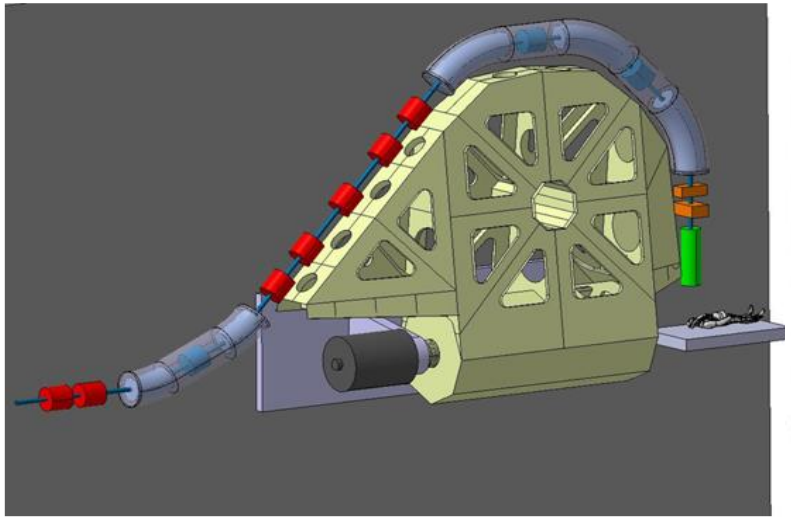
The SEEIIST facility

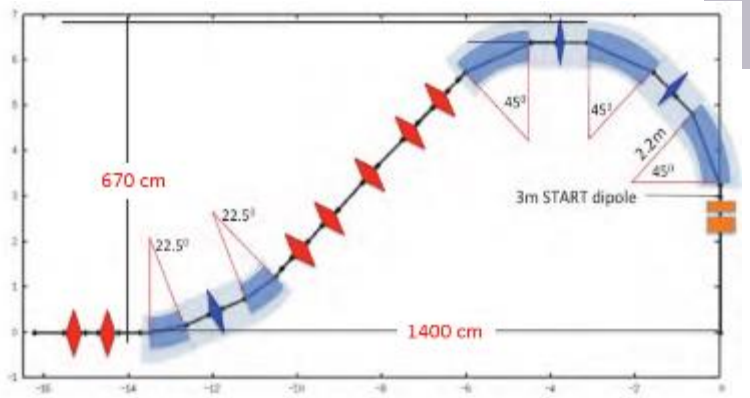
The Superconducting Ion Gantry

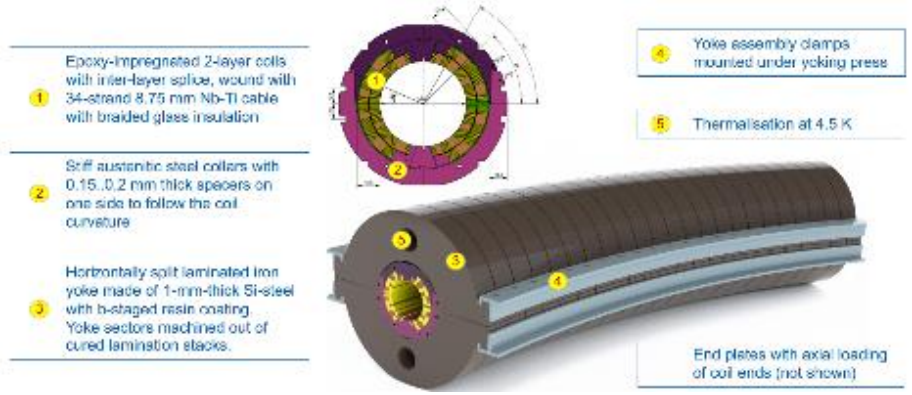
New compact (7m radius) superconducting ion gantry rotating around the patient for ≈±100^0, equipped with curved superconducting magnets of new design (3-5 T field) to be developed within a collaboration INFN, CERN, CNAO, MedAustron.

Mechanical design (light, without counterweight) and optics being developed within HITRI+ by a collaboration CERN, CNAO, RTU.



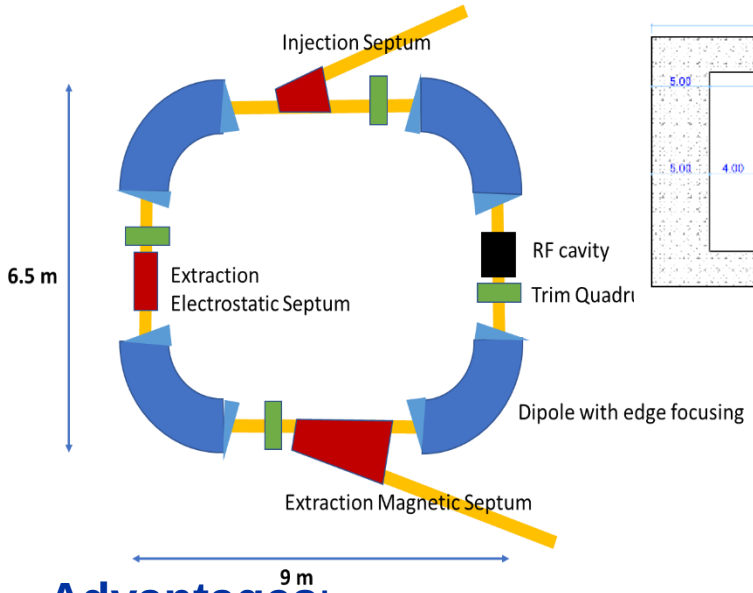


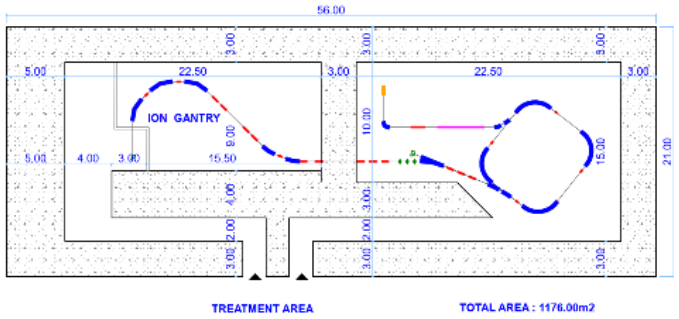




"SIGRUM, A Superconducting Ion Gantry with Riboni's Unconventional Mechanics"
U. Amaldi, N. Alharbi, E. Benedetto, P.L. Riboni and M. Vaziri, TERA Foundation
D. Aguglia, V.Ferrentino, G. Le Godec, M.Karppinen, D. Perini, E.Ravaioli and D. Tommasini,
CERN-ACC-NOTE-2021-0014 ; NIMMS-Note-002

A compact helium synchrotron





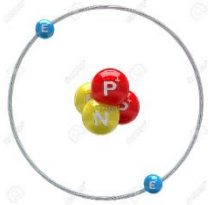
A single-room facility with compact He synchrotron and superconducting gantry

Advantages:

- Simple and compact, known technologies
- Synchrotron based on standard components
- Can use SC gantry under development.

Disadvantages:

- Cannot exploit the full potential of ions
- Requires some limited R&D for the magnets



M. Vretenar, D. Tommasini, E. Benedetto, M. Sapinski, A Compact Synchrotron for Advanced Cancer Therapy with Helium and Proton Beams, submitted at IPAC22

The NIMMS collaboration has started the design of a compact Helium synchrotron

- New 2T magnets, 220 MeV/u for 4He2+ (30 cm range, rigidity 4.5 Tm).
- Can operate with 12C up to 10 cm penetration.
- Slow (RF ko) and “Flash” extraction, microbeams.
- Online imaging with protons or prompt gamma.

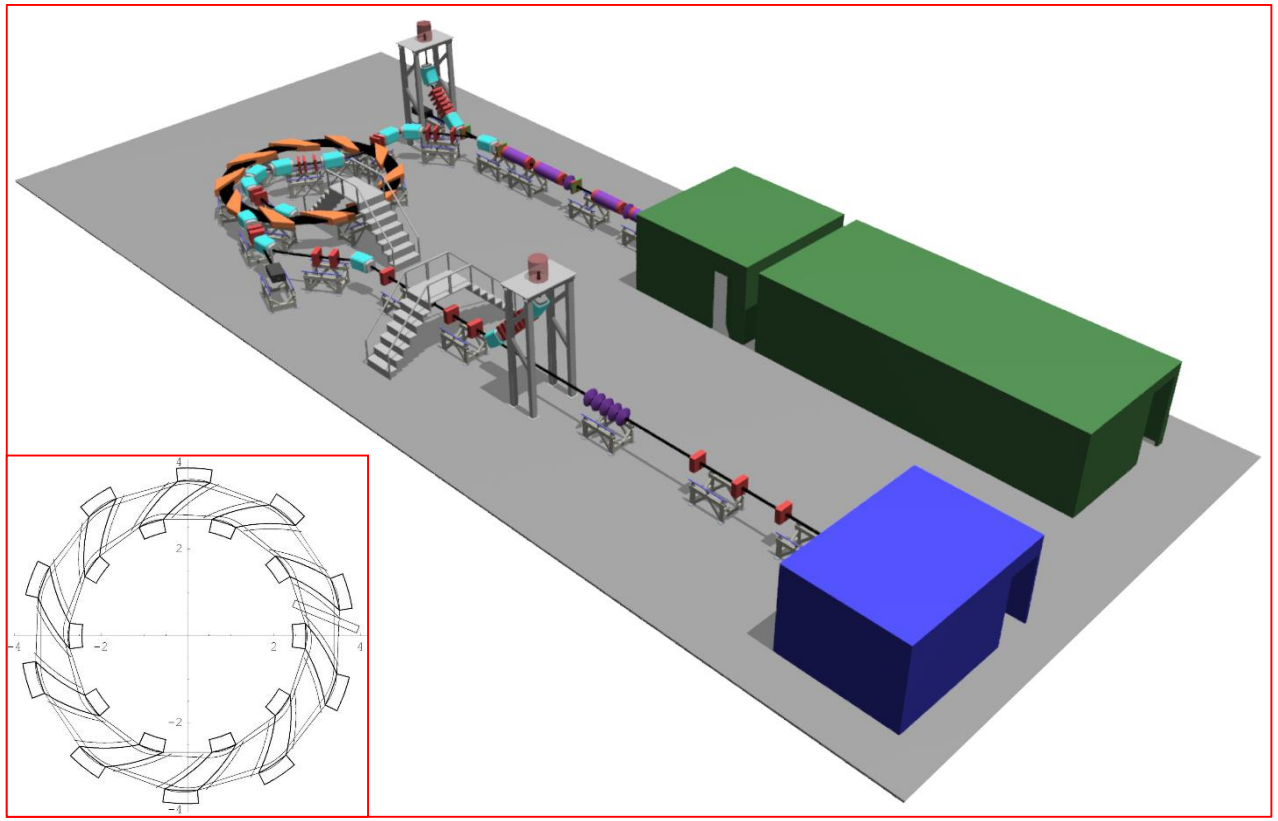
Helium gives better precision than protons and could treat some radioresistant tumours at much lower cost than carbon – wide interest in medical physics community. Tests starting at HIT.

Limited R&D required (2T magnets).

Can use the SIGRUM gantry at a lower field (safer)

Well adapted for a programme of parallel therapy with protons and research with helium aiming at its medical licensing.

The Ion Therapy Research Facility concept



LhARA (Laser-hybrid Accelerator for Radiobiological Applications) collaboration coordinated by Imperial College:

- Innovative laser ion source
- Gabor lens for beam capture
- FFAG accelerator technology

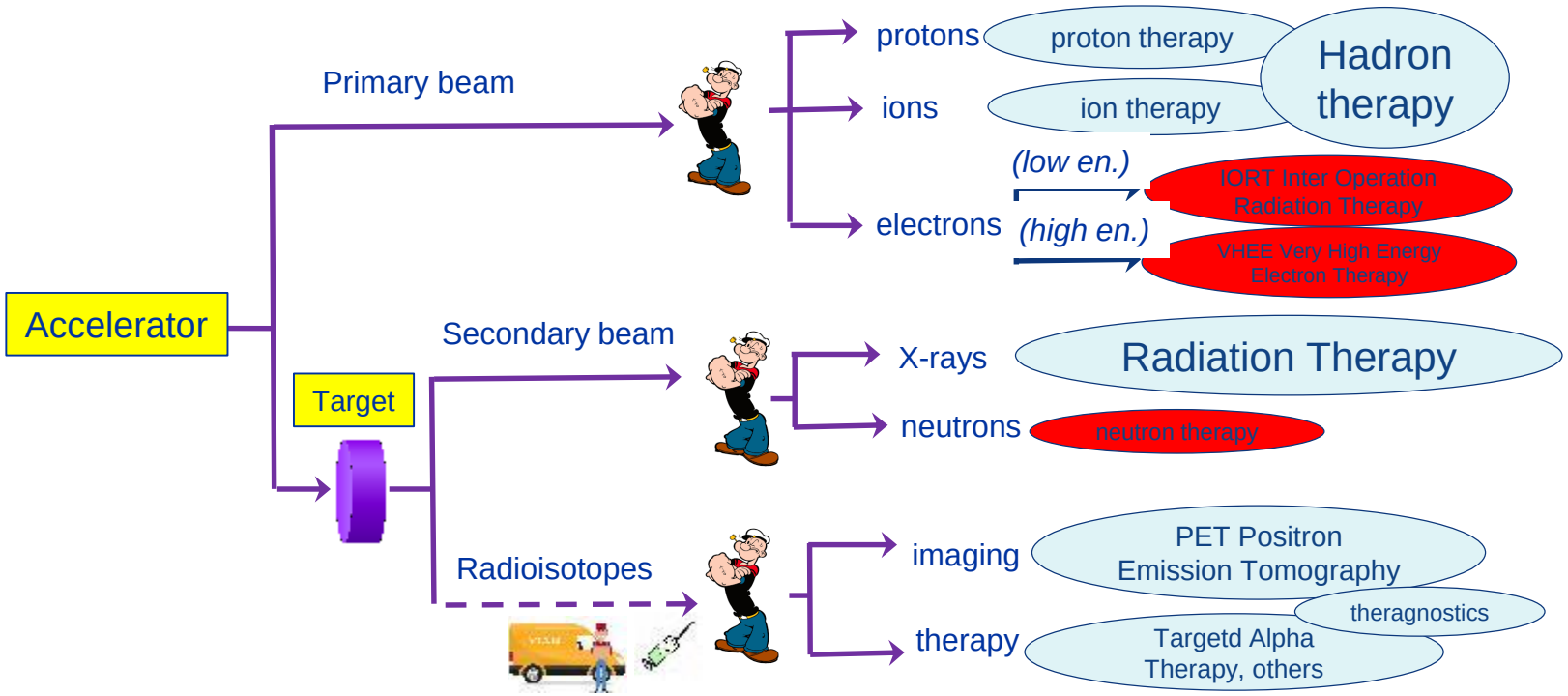
Ion Therapy Research Facility proposal

- Innovative and challenging accelerator
- No patient treatment, only research programme (no need to licence for medical use, no constraints and risks with patients).

Innovative, with strong potential, requires robust R&D effort to demonstrate laser-driven source

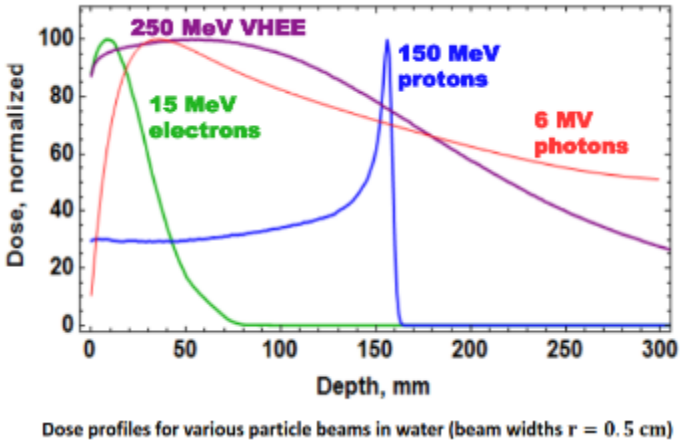
Complementary with the NIMMS programme

3 – electrons and neutrons

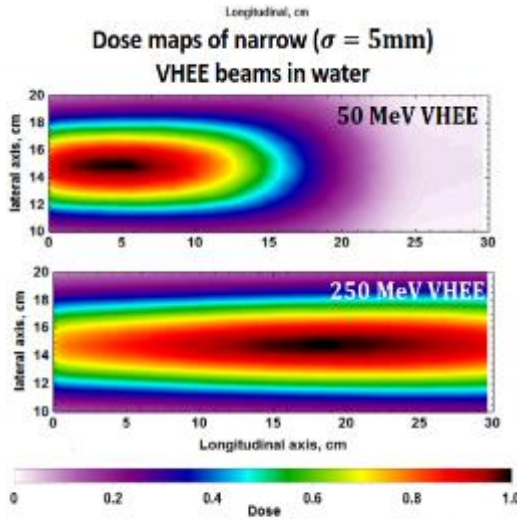


Electrons: IORT and VHEE

Inter Operational Radiation Therapy (IORT) – (5-20 MeV):
Technique derived from radiation therapy, where a compact electron linac is not used to produce X-rays, but to send the electrons directly on the tissues.
It delivers a concentrated dose of radiation therapy to a tumour bed during surgery. This technology may help kill microscopic diseases, reduce radiation treatment times, preserve more healthy tissue.



Dose profiles for various particle beams in water (beam widths r = 0.5 cm)

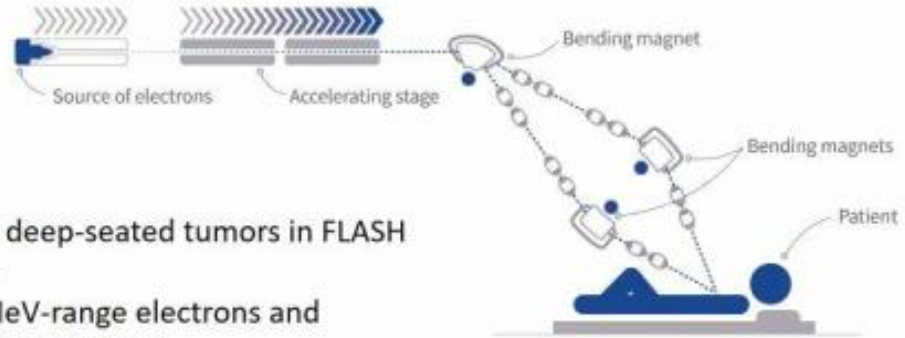


Dose maps of wide (σ = 20mm)
VHEE beams in water

Very High Energy Electrons (50-250 MeV) for radiotherapy:
Proposed as a lower-cost alternative to hadron therapy, treat deep seated tumours with high-energy electron beams. High dose deposition, less sensitive to errors, good sparing of healthy tissues.
Made possible by recent advances in high-gradient NC linac technology (CLIC, etc.).

FLASH with electrons – a new avenue to radiation therapy

CLIC technology for a FLASH facility being designed in collaboration with CHUV



Treat large, deep-seated tumors in FLASH conditions.
Uses 100 MeV-range electrons and optimized dose delivery.
Compact to fit on a typical hospital campus.

Construction of the prototype

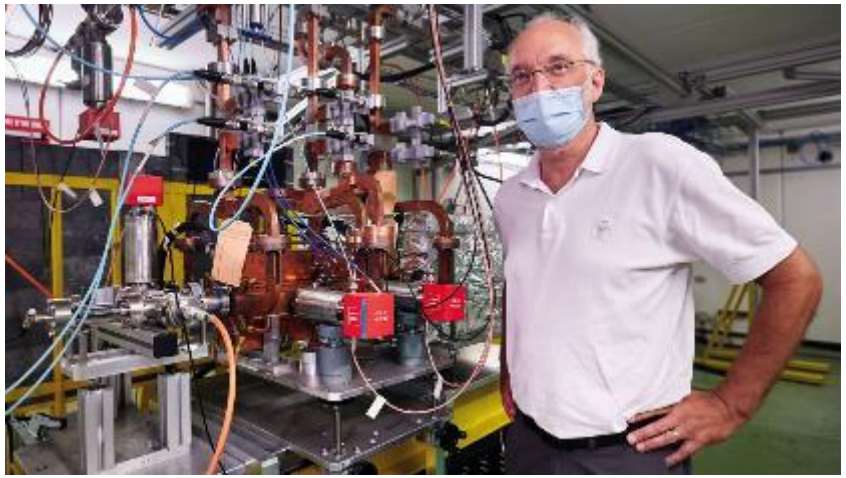
Installation 2023

First patient
2024-25

Lausanne University Hospital and CERN collaborate together on a pioneering new cancer radiotherapy facility

Lausanne University Hospital (CHUV) and CERN, in Switzerland, are collaborating to develop the conceptual design of an innovative radiotherapy facility, used for cancer treatment. The facility will capitalise on CERN breakthrough accelerator technology applied to a technique called FLASH radiotherapy, which delivers high-energy electrons to treat tumours. The result is a cutting-edge form of cancer treatment, highly targeted and capable of reaching deep into the patient's body, with less side-effects. The first phase of the study comes to a conclusion this September.

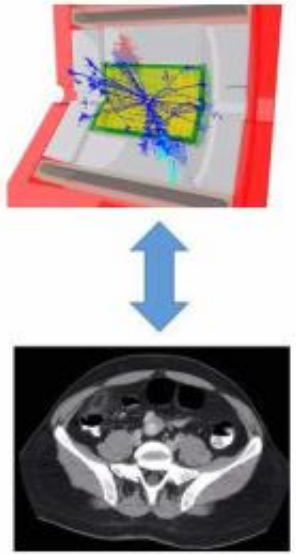
In radiotherapy, the FLASH effect appears when a high dose of radiation is administered almost instantaneously - in milliseconds instead of minutes. In this case, the tumour tissue is damaged in the same manner as with conventional radiotherapy, whereas the healthy tissue appears to be less affected, meaning that less side effects are expected.



The remarkable connection between CLIC and FLASH

Both need:

- Very intense electron beams
  - CLIC – to provide luminosity for experiments
  - FLASH – to provide dose fast for biological FLASH effect
- Very precisely controlled electron beams
  - CLIC – to reduce the power consumption of the facility
  - FLASH – to provide reliable treatment in a clinical setting
- High accelerating gradient
  - CLIC – fit facility in the Geneva area and limit cost
  - FLASH – fit facility on a typical hospital campus and limit cost of treatment



Neutrons: Boron Neutron Capture Therapy (BNCT)

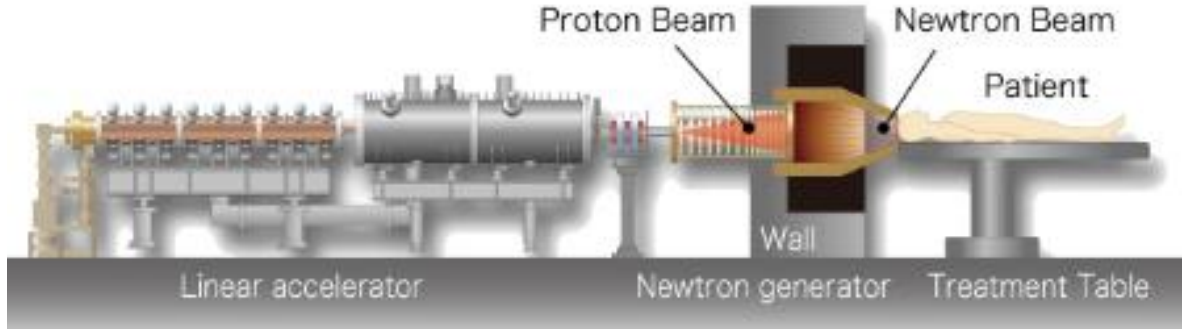
Boron Neutron Capture Therapy

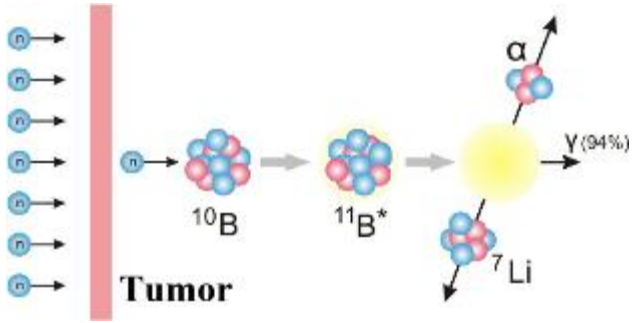
The (normal) stable version of boron, boron-10, captures slow neutrons to give boron-11. This then decays into lithium-7 and alpha particles, which kill any surrounding malignant tissue.

A boron-containing drug designed to localise in cancerous cells is injected into the patient, and a beam of low-energy neutrons shaped to optimise capture by the injected boron is directed at the cancerous sites.

Two-stage creation of the delivered dose, particularly effective with some difficult-to-treat cancers such as brain tumours or malignant melanoma.

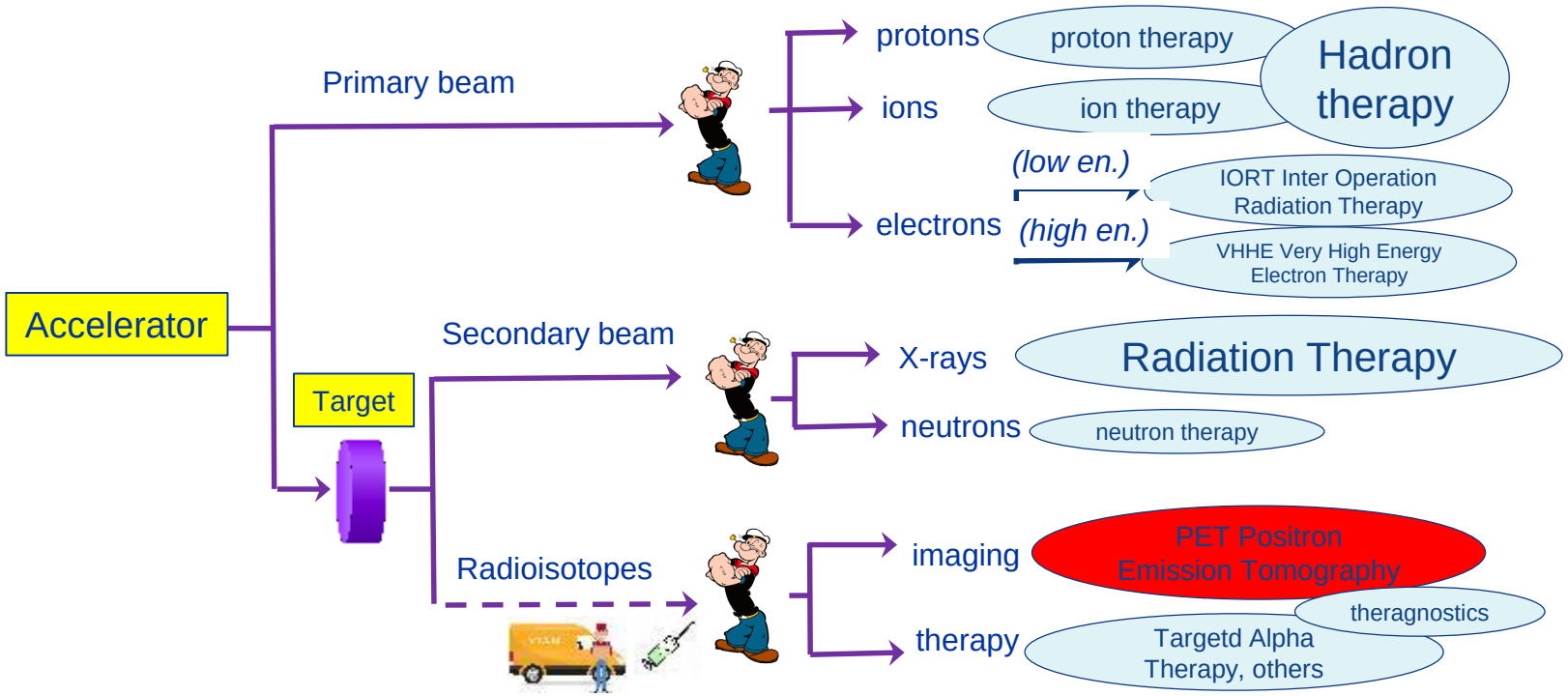
Neutron production requires intense proton beams (e.g. 3 MeV, >1 mA CW) with problems of heat load, activation, target (usually solid lithium).



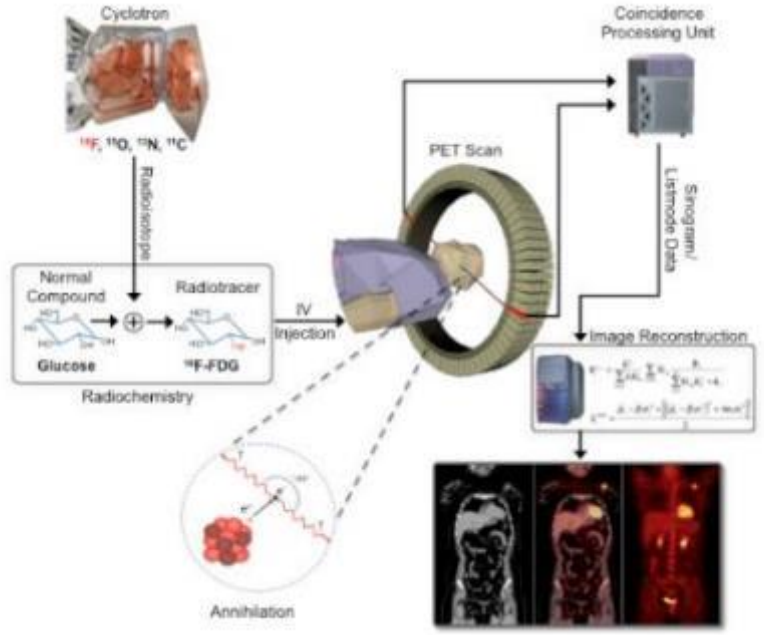


A BNCT centre is in operation in Tokyo, a first commercial unit installed at Helsinki, experimentation progressing in several centres.

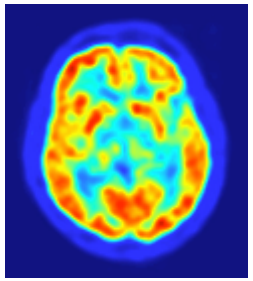
4- Radioisotopes - imaging



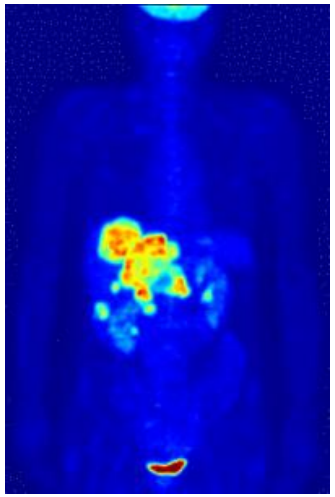
Radioisotope-based tomographies



(source: Huntsman Cancer Institute)

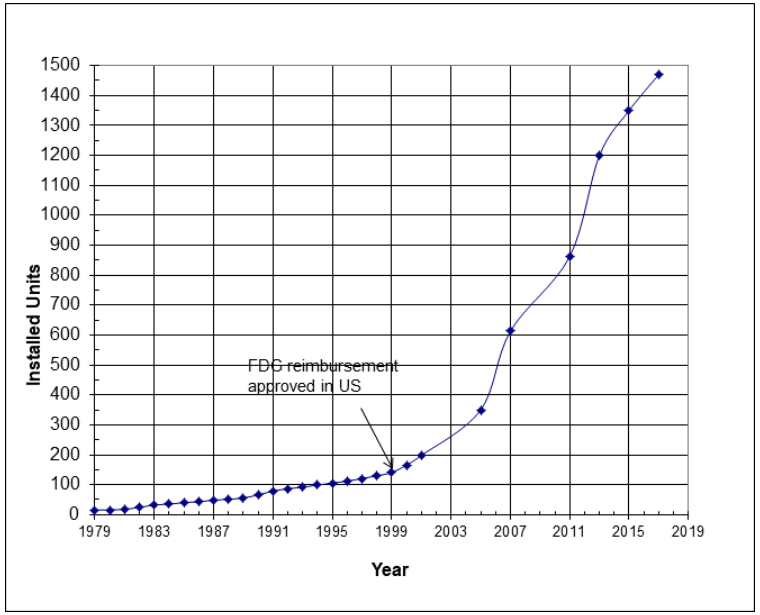


90% of PET scans are in clinical oncology



- A **radioisotope** (radiotracer) is produced by an accelerator (usually a cyclotron) and attached to a normal chemical compound, usually a glucose, in a radiopharmaceutical unit.
- The compound is injected to the patient and accumulates in tissues with high metabolic activity, as tumours – and metastasis.
- When the radioisotope decays, the emitted particles are detected by a scanner allowing a precise mapping of the emitting areas.
- In **SPECT** (single photon emission computed tomography) is used Technetium-99 (6 hours half-life) that emits a photon. 99-Te is generated in the hospital by Molybdenum-99 (66 hours half-life) produced at a nuclear plant.
- In the much more precise **PET** (Positron Emission Tomography) is used Fluorine-18 (1h50' half-life) attached to Fludeoxyglucose (FDG) molecules, which emits positrons that annihilates with electrons producing 2 gamma rays in opposite directions.

The isotope production and distribution scheme

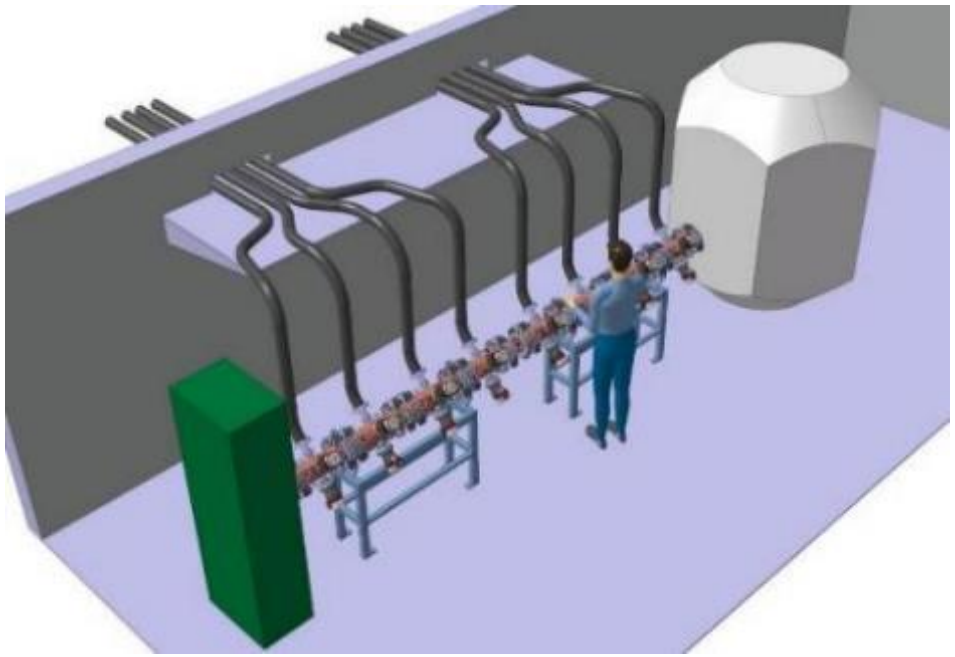


(courtesy Robert Hamm)

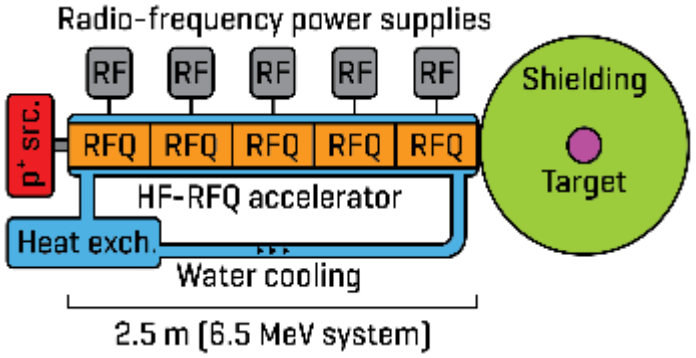
Isotopes and radiochemical drugs are produced in large centres equipped with a commercial cyclotron. After production, the drugs are shipped by road or air to the hospital (FDG half-life 1h50').
This scheme works well in Europe and US (good transport networks, shows limits in Asia and rest of world).

- Sales in 2015 - US$165M (~ 60 units sold per year).
- Top 5 manufacturers sell more than 50 units per year.
- PET sales dominate market (> 95% of all PET procedures use FDG.
- Sales flat (saturated?) in North America and Europe due to FDG distribution model.
- Sales increasing in Asia and rest of the world.

Radio Frequency Quadrupole for isotope production



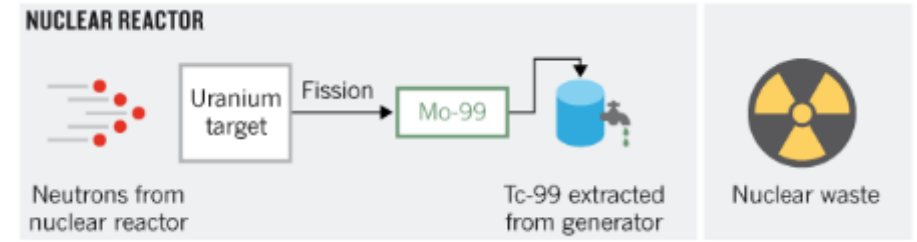
CERN has developed and built a «mini-RFQ» (Radio Frequency Quadrupole) at 750 MHz, extending to higher frequencies and applications outside science the experience of the RFQ for Linac4, the new LHC injector



Thanks to its small dimensions, simple operation, and minimum radiation to the environment, this compact RFQ design can be used for production of isotopes for PET diagnostics (18F, 11C) directly in hospitals (no need for long-distance shipping of isotopes)

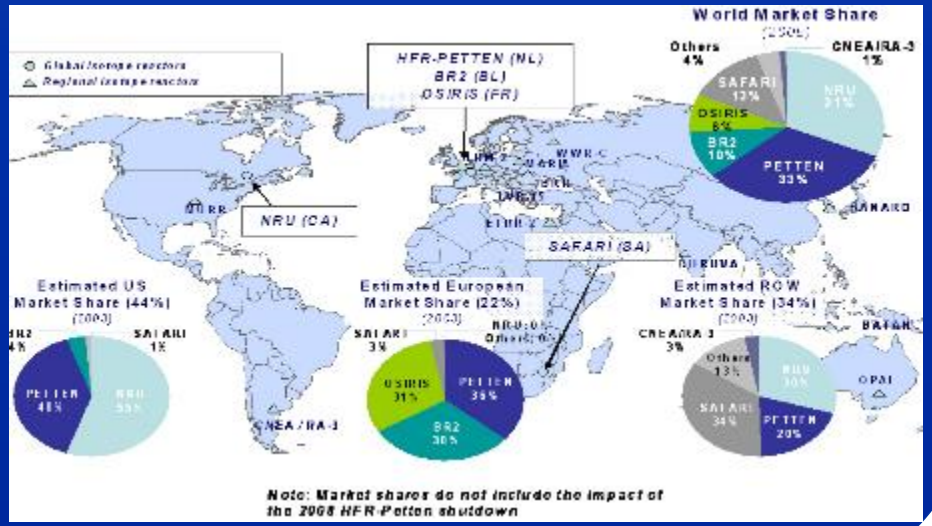
Production rate: >30 average patient doses of ^{18}F per hour

SPECT isotopes from accelerators



Source: Nature, 2013

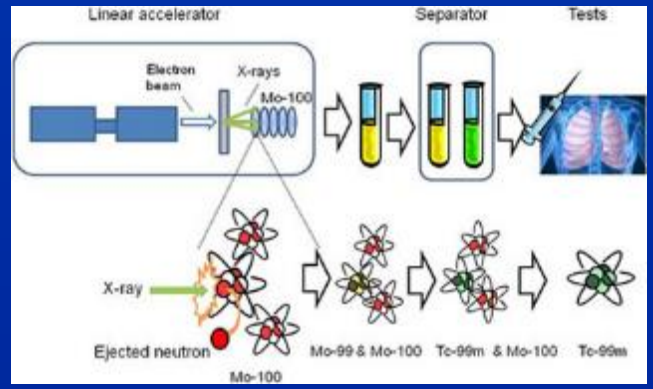
SPECT isotopes are now produced in nuclear reactors (Molybdenum-99 generators, 66 hrs., converted to Technetium-99 in the hospital).



Source: Government of Canada

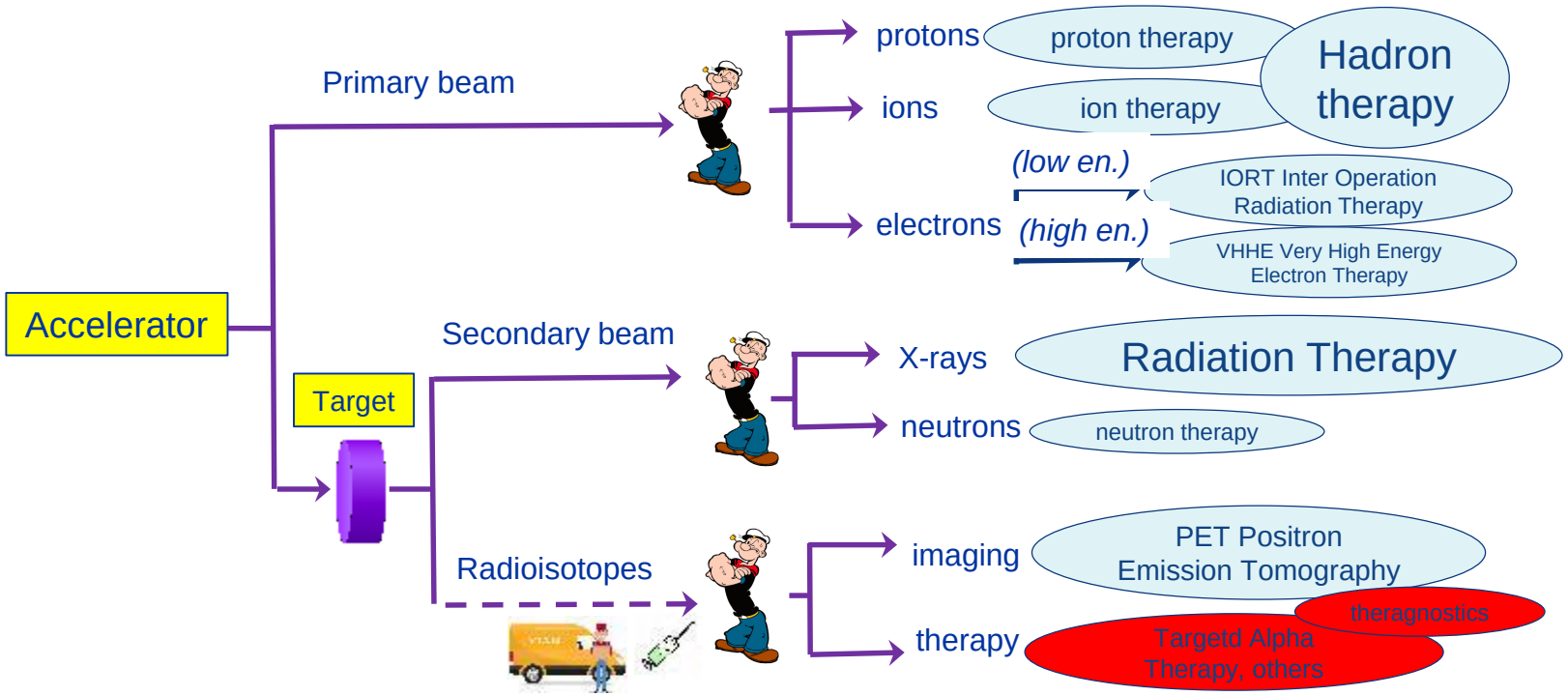
Accelerator Production of Technetium-99 (half-life 6 h)

- 30 MeV cyclotron
- Photo-fission of U
- Neutron-spallation of Mo



2009 shortage crisis

5 – Radioisotopes, treatment

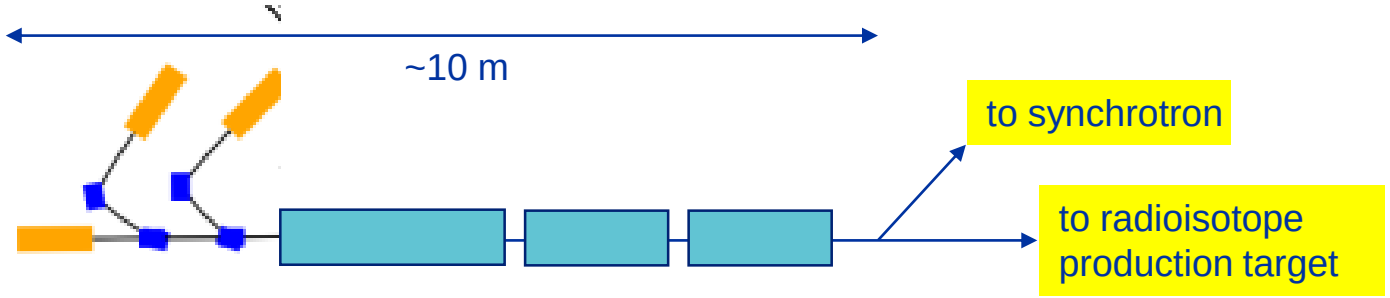


Linac for production of therapeutical radioisotopes

A new ion therapy facility should include a **new injector linear accelerator** designed for lower cost, higher efficiency, and higher beam current.

With a minor additional investment, the linac will have 2 modes of operation: for injection in the synchrotron, and for sending the beam to a target for production of medical radioisotopes.

Two frequencies being explored: 216 MHz and 325 MHz.



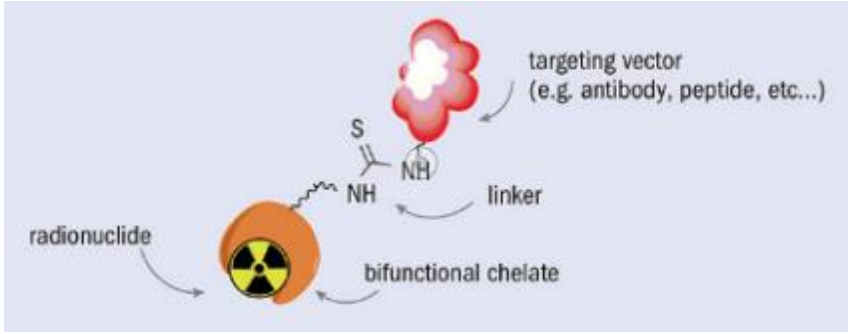
3 ion sources	Linac section1	Linac section2	Linac section3
$^{12}C^{4+}$, 600 μA $^{4}He^{2+}$, 2-5 mA p, 10 mA	q/m=1/3 W_{in}=45 keV/u W_{out}= 5 MeV/u	q/m=1/2 W_{in}= 5 MeV/u W_{out}= 7 MeV/u	q/m=1/2 or 1 W_{in}= 7 MeV/u W_{out}= 10 MeV/u

Maximum duty cycle: 10%

Preliminary linac layout, courtesy of G. Bisoffi and A. Mamaras
To be developed in the HITRI+ EU project

Isotopes being considered:

1. **211 At** for Targeted Alpha Therapy, with alpha particles.
2. 117 mSn for theragnostic and bone metastasis, with alpha particles.
3. 11 C for PET scanning, with protons.



Targeted Alpha Therapy with 211 At

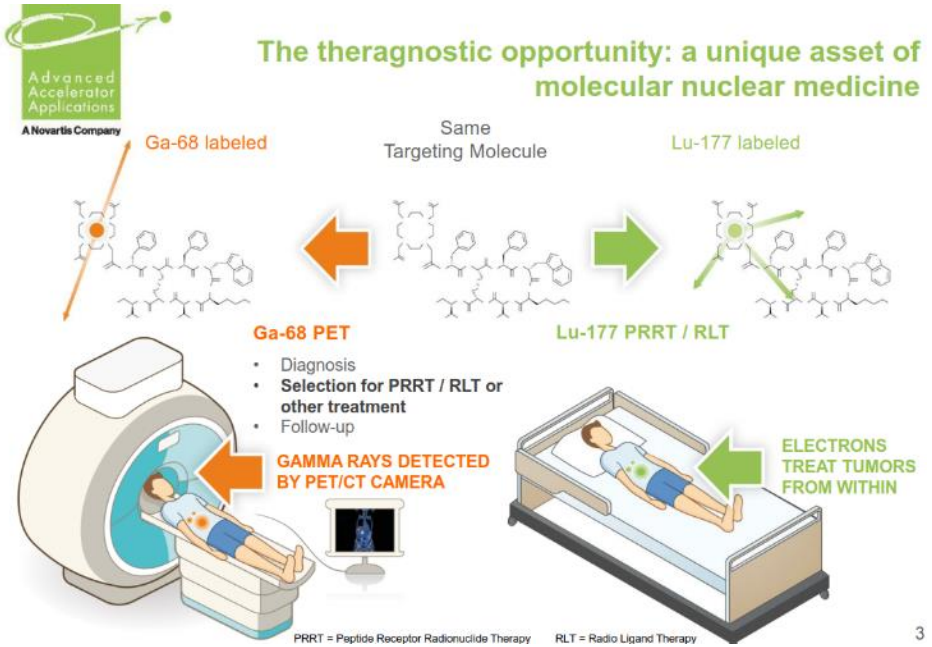
Alpha-emitting therapeutic isotopes attached to antibodies and injected to the patient: accumulate in cancer tissues and selectively deliver their dose.

Advanced experimentation, very promising for solid or diffused cancers (leukaemia).

Theragnostics

Theragnostics = integration of diagnostics and therapeutics. Disease identification, targeting, treatment and monitoring opens a new chapter in precision medicine.

In Molecular Nuclear Medicine, theragnostics consists in using targeting molecules labeled either with diagnostic radionuclides (e.g., positron or gamma emitters), or with therapeutic radionuclides (e.g., beta emitters) for diagnosis and therapy of a particular disease. Molecular imaging and diagnosis can be followed by personalised treatment utilizing the same targeting molecules. Example: gallium 68 (Ga-68) labeled tracers for diagnosis, followed by therapy using lutetium Lu-177 to radiolabel the same targeting molecule for personalized radionuclide therapy.



A recent success story:
Lutathera developed by AAA (company with old relations to CERN, based in St. Genis, near CERN).
AAA acquired by Novartis in 2018 for 3.9 billion $

Looking into the future

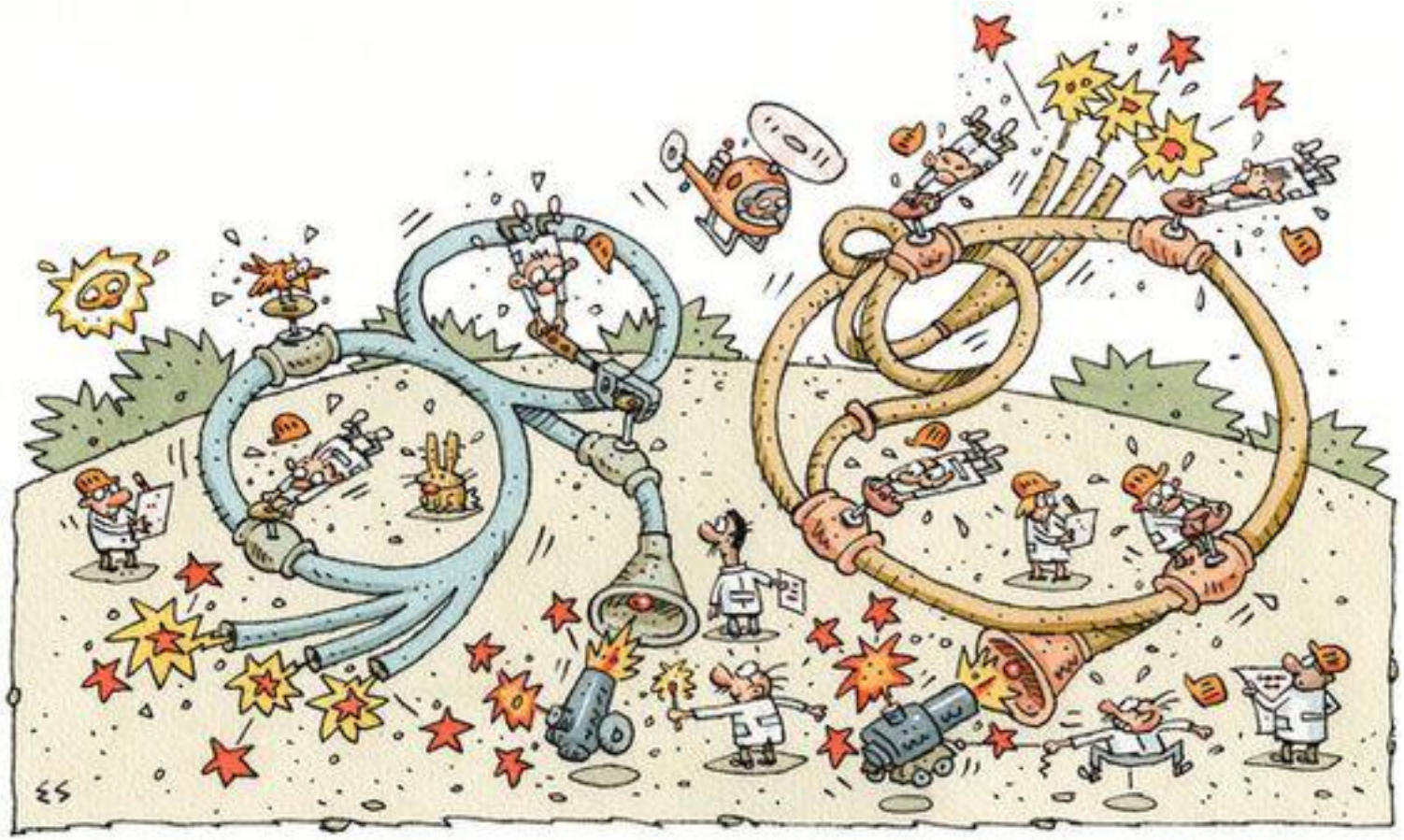
Radiation Therapy, Proton Therapy, Ion therapy, FLASH, Targeted Alpha Therapy, Immunotherapy, …

What is going to be the future landscape of our tools to fight cancer ?

A few key concepts:

- Medicine is becoming the **technology driver of XXIst century**. The development of sophisticated medical tools in particular to fight against cancer is generating a fantastic progress in all technologies, and this trend is going to continue (think of the progress in the last 50 years…).
- All the techniques that we are studying are **complementary**, with different cost and range of applications. They most likely scenario is that they will coexist, providing oncologists with a full arsenal of instruments to fight different types of cancer, to be selected on the basis of cost/benefit considerations (personalised medicine).
- The trend is clearly towards **compact systems**, controlled by **artificial intelligence** algorithms, that can act at the atomic and molecular level. **Therapy and diagnostics** are going to be more and more integrated, in the device or via “theragnostic” isotopes.

Particle accelerators will be crucial actors in this technological evolution !



End of Lecture 8

Thank you for your attention!