A review of advanced particle therapy options

Meeting on Advanced Particle Therapy Options for the Baltics

Maurizio Vretenar

CERN Project Office,
Leader of the Next Ion Medical Machine Study

CERN

nimms

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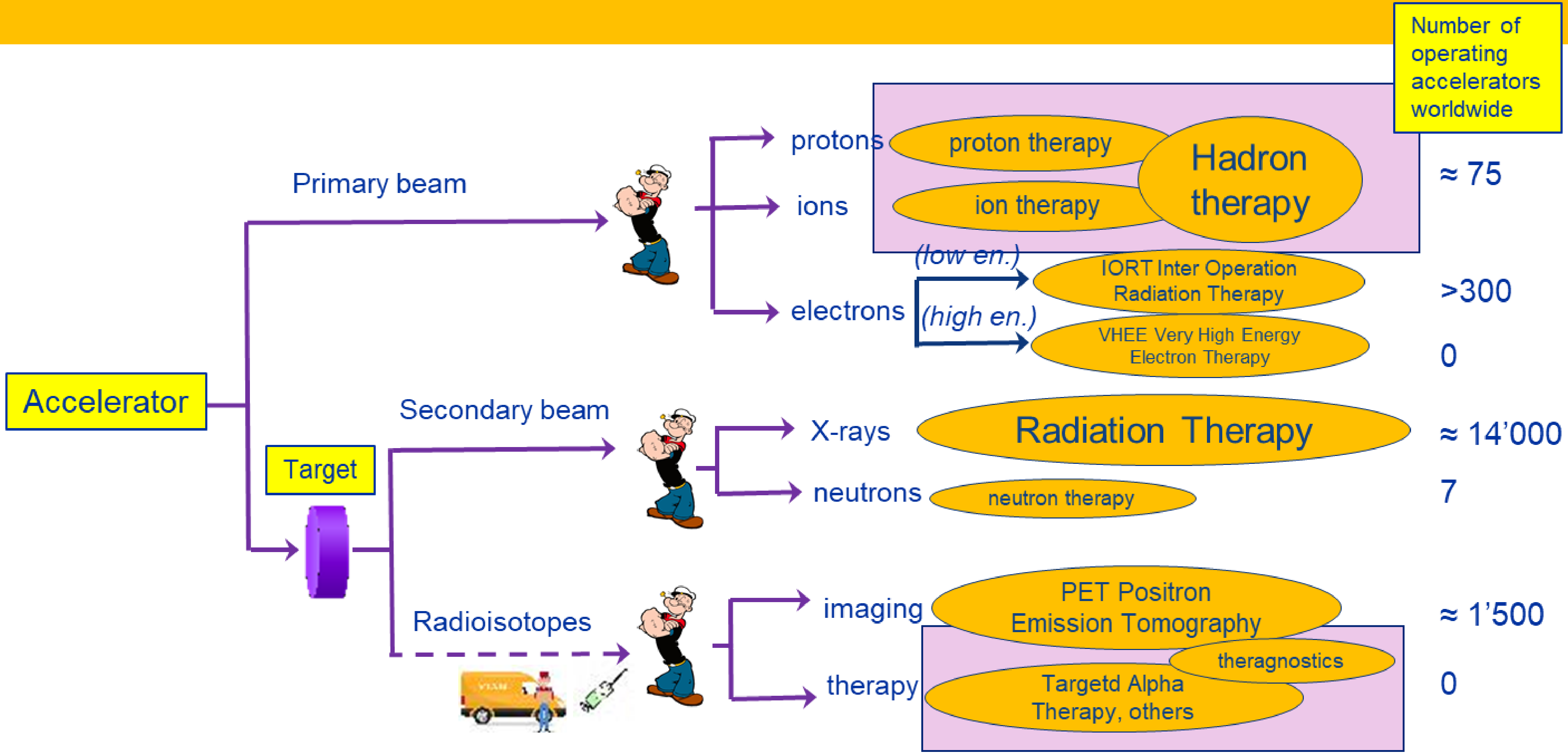
Outline

- The use of particle beams in cancer therapy – challenges and opportunities
- Present facilities and new European initiatives for particle therapy
- Review of advanced accelerator options
- Conclusions

Disclaimer: The speaker is an applied physicist with experience in design and construction of particle accelerators, who since 2017 has started approaching the medical field and developing projects at the frontier between physics and medicine. In particular for the medical and biophysics part, the judgements given in this presentation are entirely based on the personal experience and opinion of the speaker.

Particle Accelerators for Medicine



Number of operating accelerators worldwide

Accelerator

Primary beam
- protons – proton therapy – Hadron therapy – ≈ 75
- ions – ion therapy
- electrons
  - (low en.) – IORT Inter Operation Radiation Therapy – >300
  - (high en.) – VHEE Very High Energy Electron Therapy – 0

Target

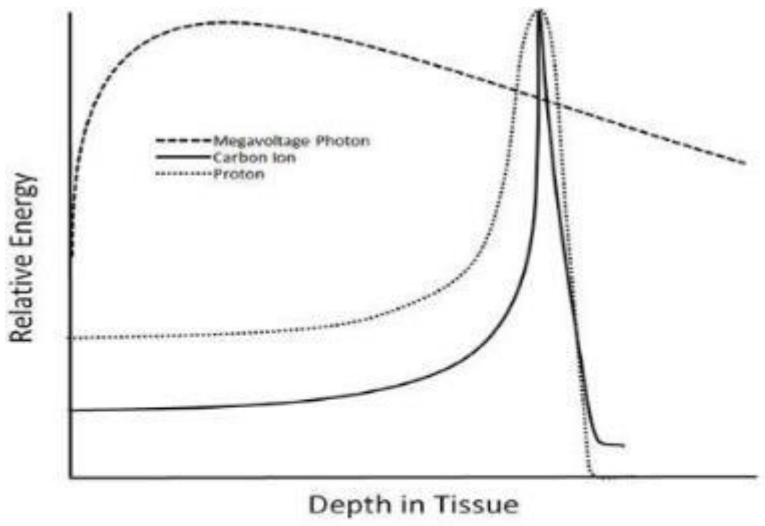
Secondary beam
- X-rays – Radiation Therapy – ≈ 14’000
- neutrons – neutron therapy – 7

Radioisotopes
- imaging – PET Positron Emission Tomography – ≈ 1’500
- therapy – Targetd Alpha Therapy, others – theragnostics – 0

Total: ≈ 16’000 particle accelerators operating for medicine

Therapy of cancer with particle beams

Goal: curing deep solid tumours with particle beams, with minimum damage to surrounding organs



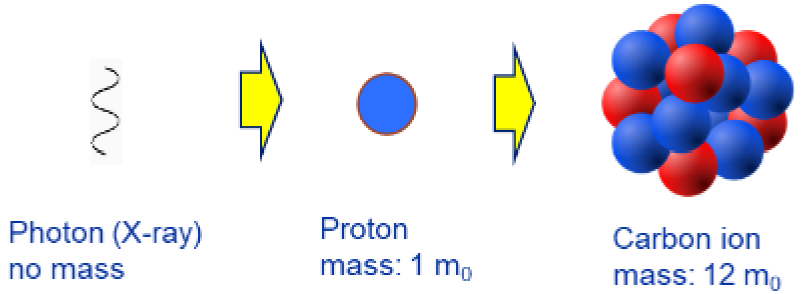
Energy deposition of X-rays, protons, carbon ions

Conventional Radiation Therapy makes use of **X-rays** that deliver most of their dose in healthy tissue before reaching the tumour.

Protons and heavier ions present a characteristic **Bragg peak:** A beam of particles starts to deposit energy at a given depth corresponding to its energy.

These techniques aim at "bloodless surgery": can destroy a cancer with minimum damage to the surrounding tissues

Because of their higher mass and energy loss in the tissues, ions act in a different way than X-rays or protons

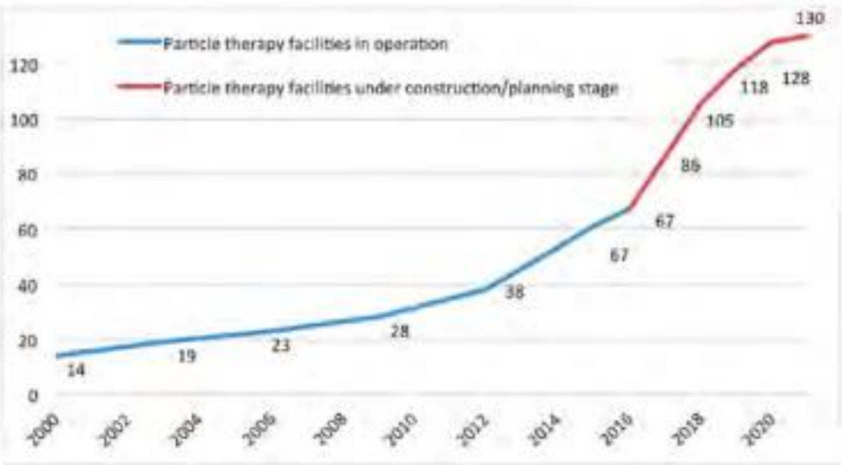


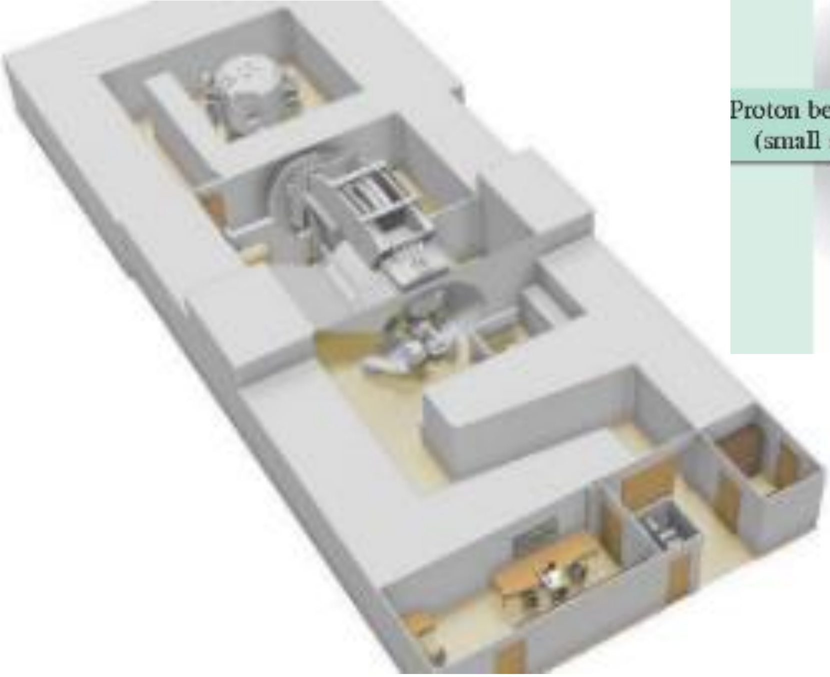
The rise of proton therapy

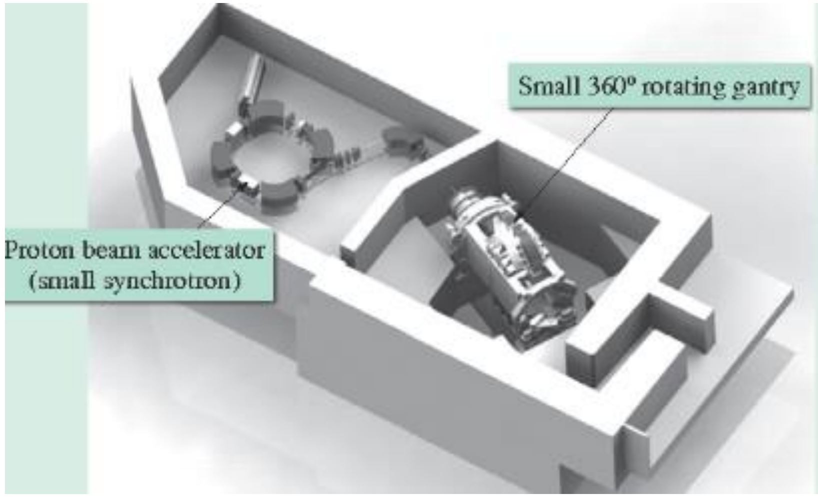
Protons have a lower energy deposition per length than ions → they need less energy to penetrate the full body → the accelerator is smaller, can be used superconducting cyclotrons or small synchrotrons

4 companies are now selling turn-key proton therapy systems at a starting cost of about 40 M€.

Fast increase in the number of facilities worldwide



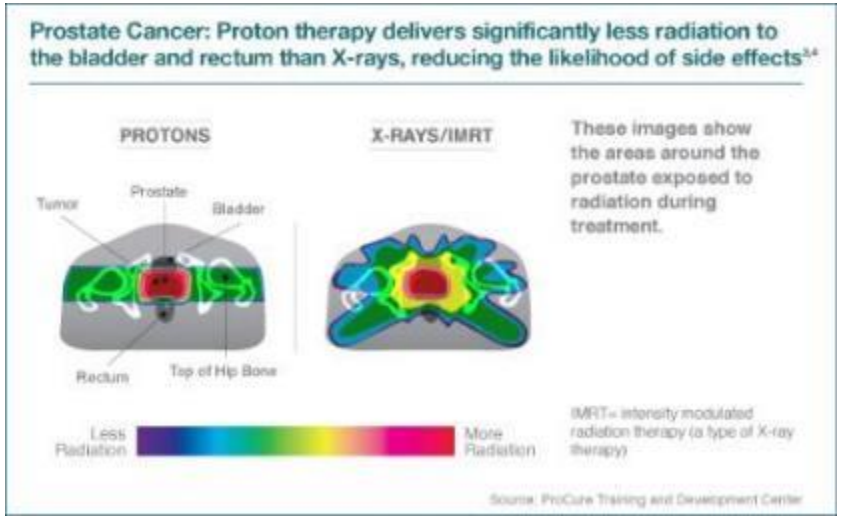




The Hitachi synchrotron system (Japan)

ProteusOne from IBA (Belgium)

Proton therapy vs. X-ray therapy



Prostate Cancer: Proton therapy delivers significantly less radiation to the bladder and rectum than X-rays, reducing the likelihood of side effects[3,4]

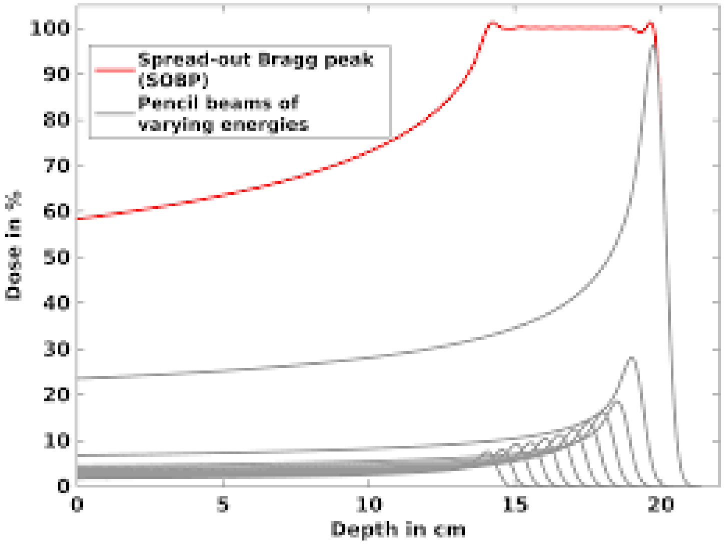
These images show the areas around the prostate exposed to radiation during treatment.

IMRT= intensity modulated radiation therapy (a type of X-ray therapy)

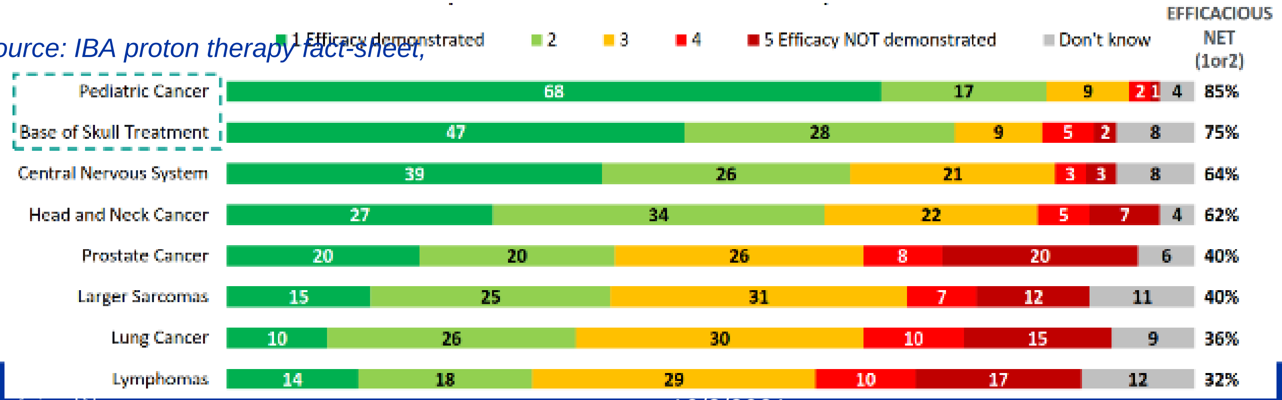
Source: ProCure Training and Development Center

Main challenges of proton (and ion) therapy:

- Treatment planning (spread-out Bragg peak)
- Moving organs
- Quantify quality of life after treatment



Proton therapy is now recommended for many types of cancer, in particular for children (lower risk of recurrencies) – covered by health insurance in most EU countries.



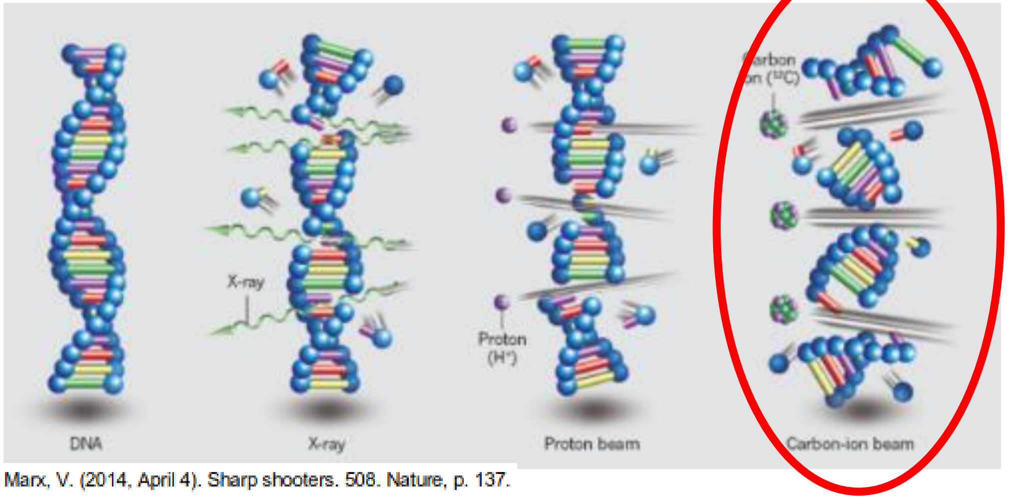
Source: IBA proton therapy fact-sheet,

New opportunities: FLASH therapy

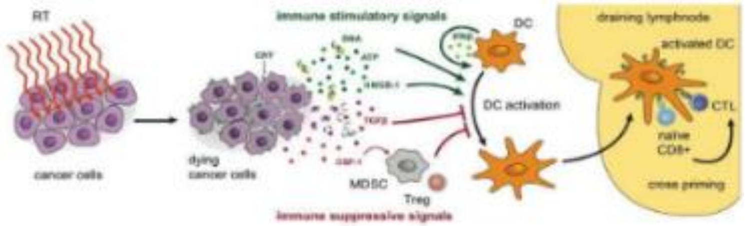
Cancer therapy with heavier ions

Heavy ions are **more effective than protons or X-rays** in attacking cancer:

1. Higher energy deposition (and ionisation) per length generates a large number of double-strand DNA breakings that are not reparable by the cell itself.
2. Energy deposition more precise, with lower straggling and scattering
3. The different damage mechanism makes ions effective on hypoxic radioresistant tumours – 1 to 3% of all RT cases (200-500 cases/year per 10M people).
4. Recent studies show that ion therapy combined with immunotherapy may be successful in treating diffused cancers and metastasis.



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



Long-term goal: the cancer vaccine

Example:
24.06.2021, experiment at GSI Darmstadt combining carbon ion therapy with **an mRNA-based cancer immunotherapy drug (vaccine)**. Combining this powerful systemic drug with localized heavy ion bombardment of the primary mass could be a key to defeat cancers in advanced stage.

Patients are treated with Carbon ions since 1994, but much **research is still needed**, in terms of optimisation of ion type, delivery modality, new techniques (flash), integration of dosimetry, etc.:
Ion treatment is still in its infancy!

Present and the future of ion therapy accelerators

Ions deliver more energy to the tissues, but need more energy to enter the body → a larger accelerator (430 MeV/u for Carbon compared to 250 MeV/u for protons)

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

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

Layout of the Heidelberg Ion Therapy facility

Particle accelerator technology has made a huge progress in the last 20 years, in particular towards developing new more compact and less expensive accelerator designs.

We can today explore new accelerator designs profiting of the latest advances in accelerator technologies.

All ion facilities worldwide operate with Carbon but there is a strong interest in **lighter ions like Helium** that could keep the advantages of carbon but require a smaller machine.

The CERN Next Ion Medical Machine Study (NIMMS)

Requirements of the ion therapy community, expressed at the Archamps Workshop, June 2018

1. **Concentrate on heavy ions** (Carbon but also Helium, Oxygen, etc.).

2. **A next generation ion accelerator must have:**

☐ Lower cost and footprint, compared to present;
☐ Faster dose delivery with higher beam intensity or pulse rate, and possibly FLASH
☐ A gantry device to precisely deliver the dose to the tumour.
☐ Operation with multiple ions, for therapy, research, and dose optimisation.

Establishment of NIMMS, the
Next Ion Medical Machine Study at CERN (2018):

- Building on the experience of the PIMMS (proton-ion medical machine study) of 1996/2000;
- Federating a large number of partners to develop designs and technologies for next-generation ion therapy;
- Partners can use the NIMMS technologies to assemble their own optimized facility.

Geography of particle therapy in Europe

Particle therapy centres in Europe. Courtesy of ENLIGHT, 2020

Only 2 areas in Europe without particle therapy facilities:
- South East Europe
- Baltics

Per end of 2020 more than 290'000 patients have been treated worldwide with Particle Therapy,

close to 250'000 with protons, close to 40'000 with C-ions and about 3'500 with He, pions and with other ions.

New European initiatives in ion therapy - SEEIIST

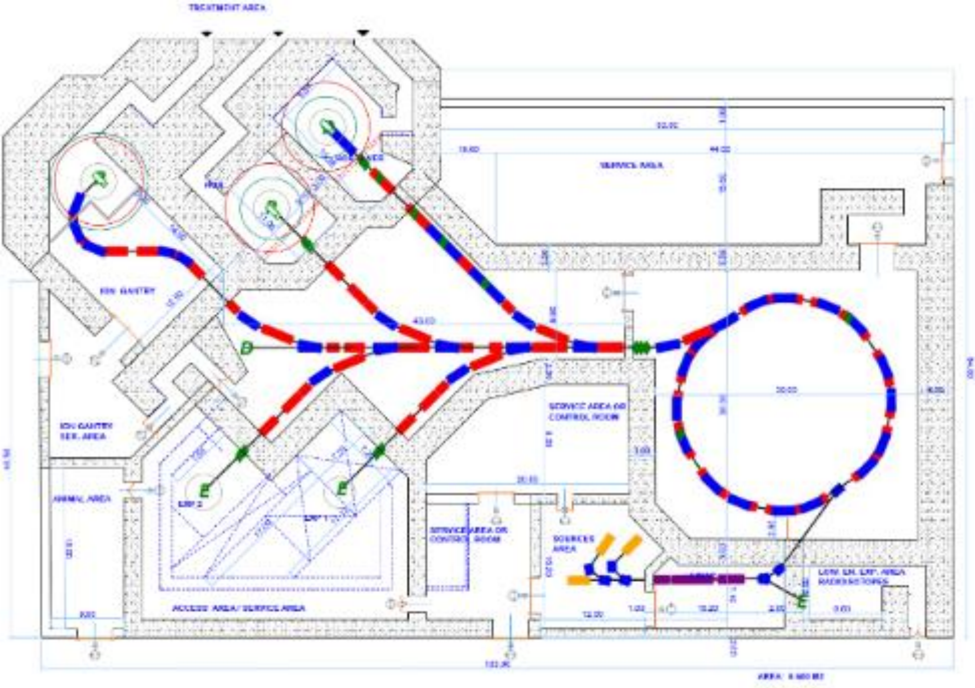
- The **SEEIIST** (South East Europe International Institute for Sustainable Technologies) is a new international partnership aiming at the construction of a new Research Infrastructure for cancer research and therapy in South East Europe (10 member countries).
- SEEIIST is supported by the European Commission, to develop the facility design in collaboration with CERN.
- Goals are to develop a new advanced design and to build international cooperation and scientific capacity in a region that will join EU but is less develop and still divided, in the line of “science for peace”.
- Promoted by H. Schopper, former Director General of CERN, and S. Damjanovic, former Minister of Science of Montenegro.

Basic concepts for a
SOUTH-EAST EUROPE
INTERNATIONAL INSTITUTE FOR
SUSTAINABLE TECHNOLOGIES
(SEEIIST)

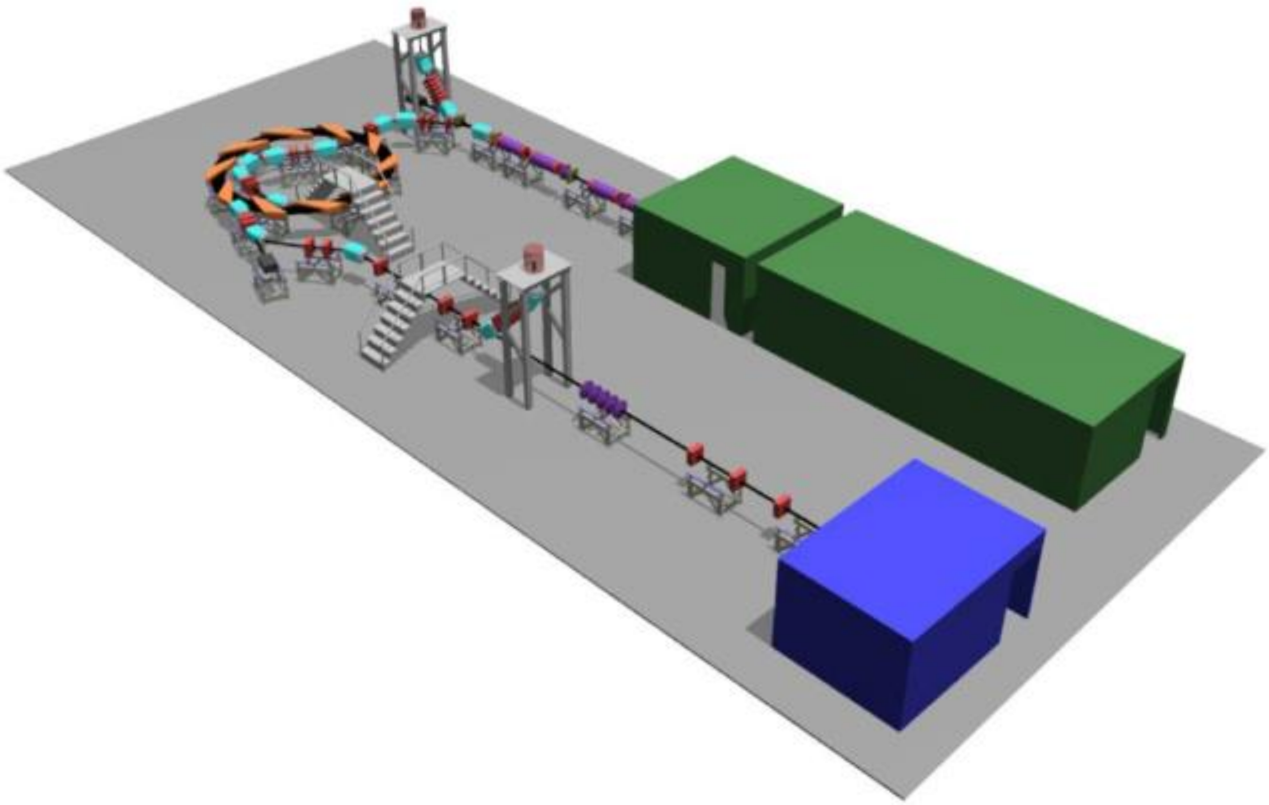
January 15, 2018

SEE ST
South East European
International Institute
for Sustainable Technologies

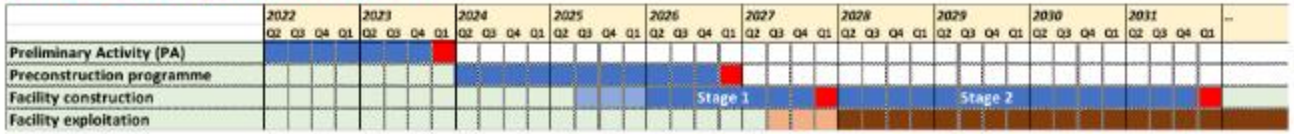
Accelerator: a large normal-conducting synchrotron
Estimated cost of facility: 240 M€



New European initiatives in ion therapy - UK



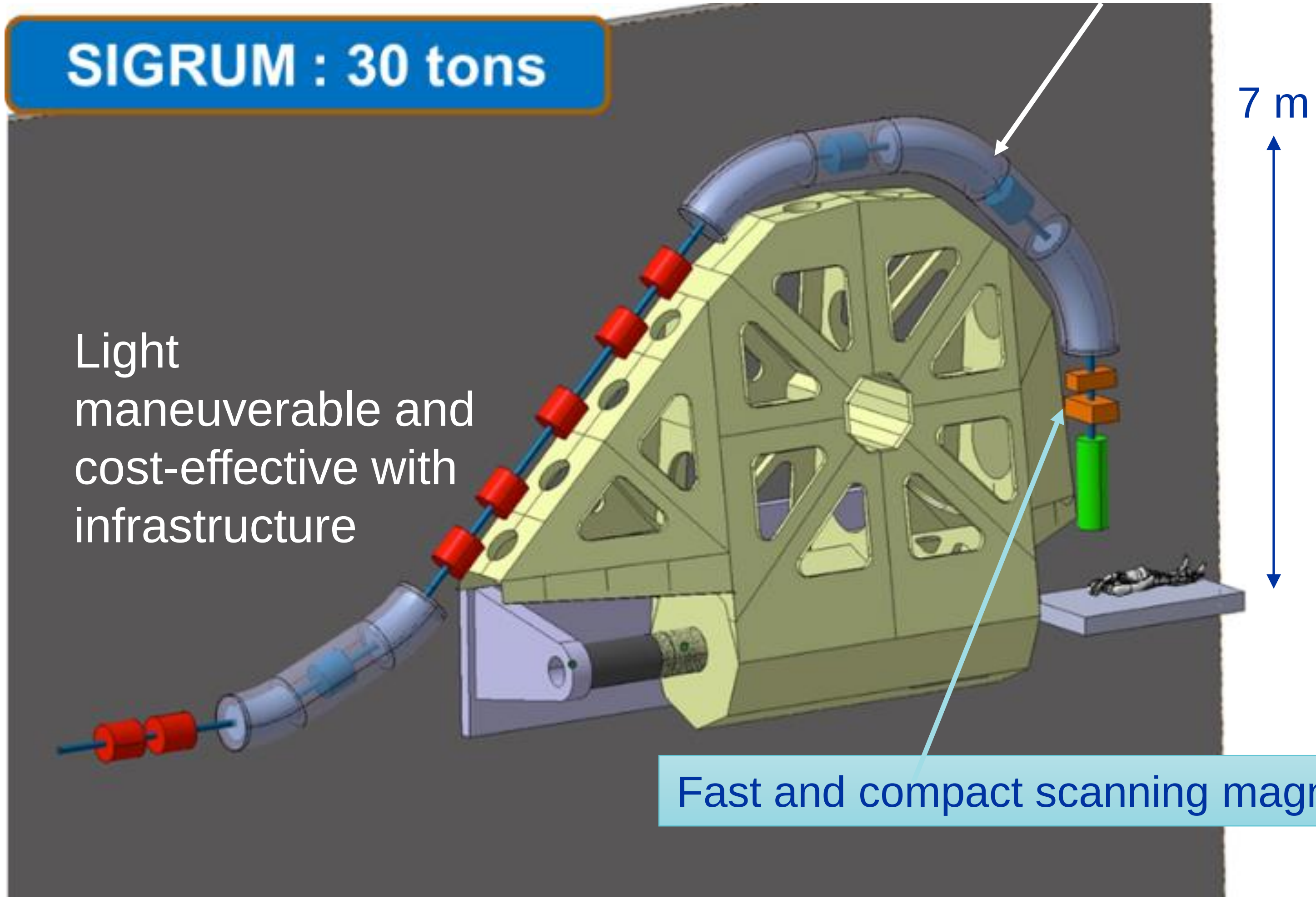
2. ITRF development timeline



Ion Therapy Research Facility

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

New European initiatives in ion therapy – the gantry



Novel CURVED SC dipole of 4- 5 T

SIGRUM : 30 tons

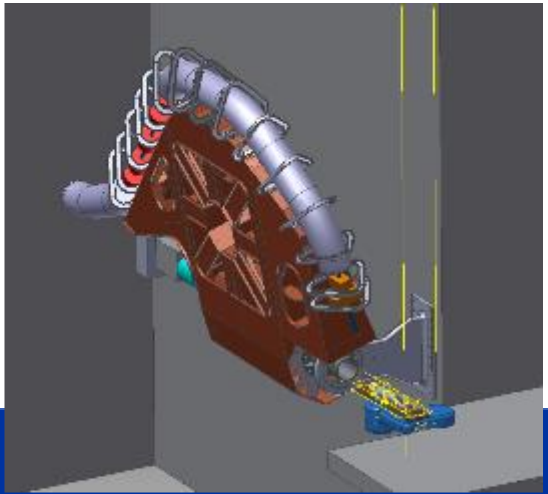
Light maneuverable and cost-effective with infrastructure

Fast and compact scanning magnets

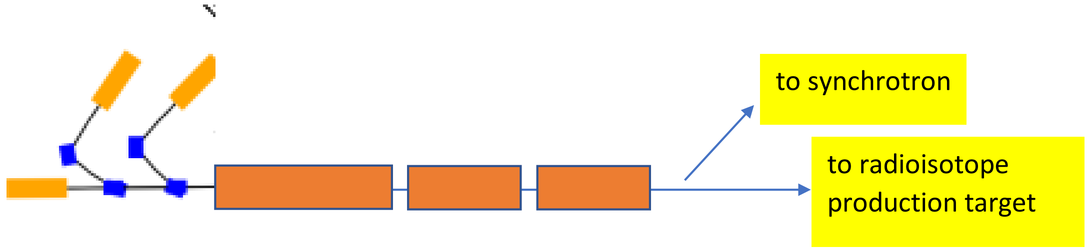
Development of a rotating Superconducting Gantry for Carbon ions (SIGRUM, proposed by TERA/CERN)

Supported by 2 collaborations:

- CERN-INFN-CNAO-MedAustron for development of SC magnets, dose delivery, range verification (2022/25, 1.6 M€). To include scanning system.
- HITRI+ EU project Task 7.5, RTU, CNAO, SEEIIST, CERN (2021/25, 314 k€, 175 k€ from RTU) for optics and mechanics design.



New European initiatives – the dual-mode linac



3 ion sources
$^{12}C^{4+}$, 600 μA, 0.2-0.3 π mm mrad
$^{4}He^{2+}$, 2-5 mA, 0.2-0.4 π mm mrad
P or H_2^+, 5 mA, 0.2-0.3 π mm mrad
(emittances rms normalised)

Linac section1
q/m=1/3
W_{in}=20 keV/u
W_{out}= 5 MeV/u

Linac section2
q/m=1/2
W_{in}= 5 MeV/u
W_{out}= 7.1 MeV/u

Linac section3
q/m=1/2 or 1
W_{in}= 7.1 MeV/u
W_{out}= 10 MeV/u

Maximum duty cycle:
10%

Version 1 : 217 MHz
Version 2 : 352 MHz

Development of a dual-mode linear accelerator (linac) for parallel injection into a synchrotron and production of medical radioisotopes.

- Collaboration CERN-U. Frankfurt-INFN in the HITRI+ EU project.
- Production and initial acceleration of He or C for synchrotron injection,
- Production of He (alpha particles) and protons for production of medical radioisotopes for therapy and imaging (those not easily produced with cyclotrons)

Three isotopes being considered:

1. 211 At for Targeted Alpha Therapy, with alpha particles.
2. 117 mSn, for theranostic, arthery plaque and bone malignancies, with alpha particles.
3. 11 C for PET scanning, with protons.

Options for the Baltics

- A commercial proton therapy system, or
- **A more advanced facility that could open the way to new ion therapy treatments,** providing one or more of the options below:
  - Treatment of patients with protons, Helium, and possibly Carbon;
  - A research programme on cancer therapy with particle beams (and isotopes)
  - Parallel production of radioisotopes for imaging and therapy;
  - New beam delivery techniques like FLASH;

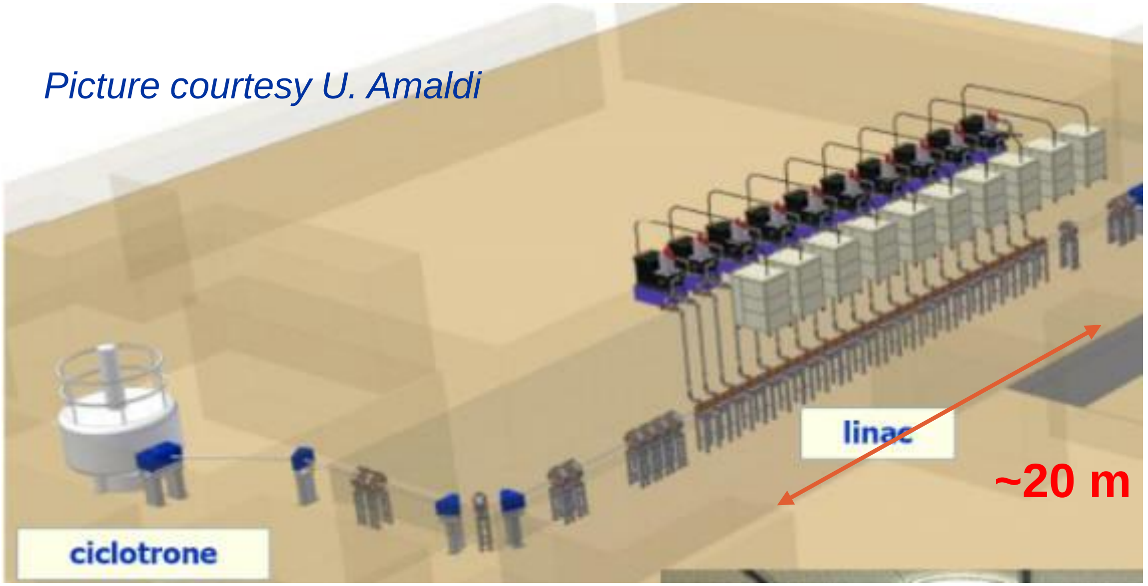
And:

- avoiding competition with existing projects
- at an acceptable cost
- providing a frame for regional (Baltic) and international collaboration

5 basic options:

1. The **cyclinac**
2. The **Carbon linac**
3. The **Helium synchrotron**
4. The **Carbon synchrotron**
5. The **superconducting Carbon synchrotron**

1. Cyclinac



Picture courtesy U. Amaldi

(Old) idea by U. Amaldi, being reconsidered by Portugal planning to install an “experimental” proton therapy accelerator at University of Coimbra

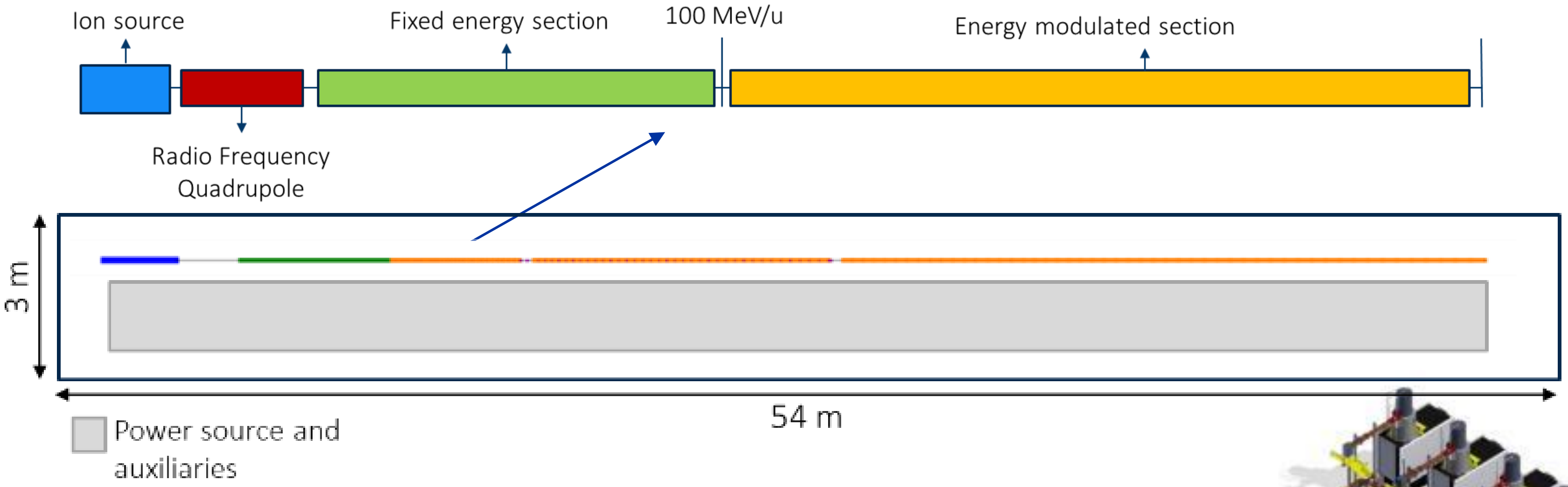
- A commercial cyclotron (30 MeV) for protons produces radioisotopes,
- One of the extracted beams feeds a compact high-frequency (3 GHz) linear accelerator in 2 sections: 70 MeV (eye treatment), 210 MeV (proton therapy).

Was never built – designs and prototypes for accelerating cavities exist (ADAM/AVO, TERA, Cockcroft Inst.) – to be calculated radiation issues related to high beam loss at the transfer cyclotron/linac (90% of beam)

Advantages:
- Modular (can be built in stages)
- Large use of commercial elements (cyclotron, cavity units)
- Fast energy variation (longitudinal scan of tumour)

Disadvantages:
- High beam loss at transfer cyclotron/linac
- No gantry design exists (with large energy acceptance)
- The final product will have a higher cost than a commercial proton unit

2. Carbon linac

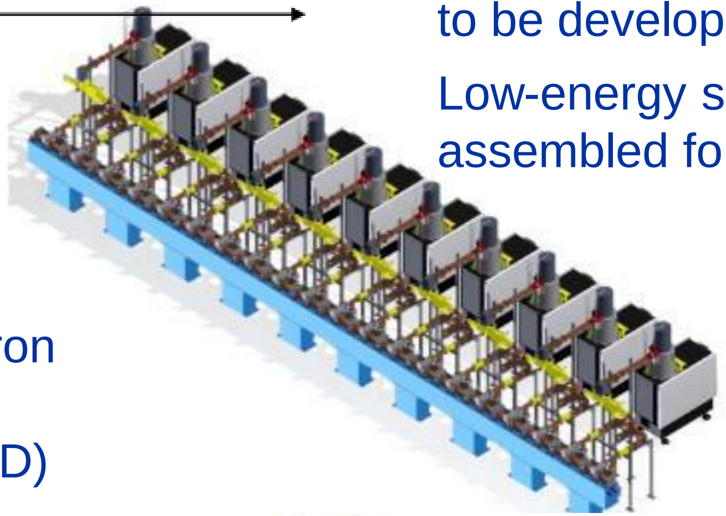


Amaldi's idea, part of NIMMS (A. Lombardi, CERN)

- can accelerate protons, He, C.
- no radioisotopes

Never built – high-energy part similar to LIGHT p-linac of ADAM/AVO, fixed energy section to be developed.

Low-energy section being assembled for testing at CERN

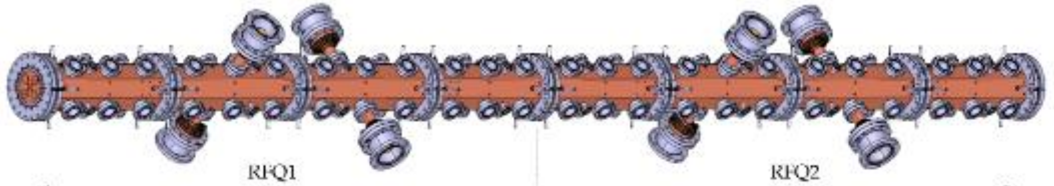


Advantages:

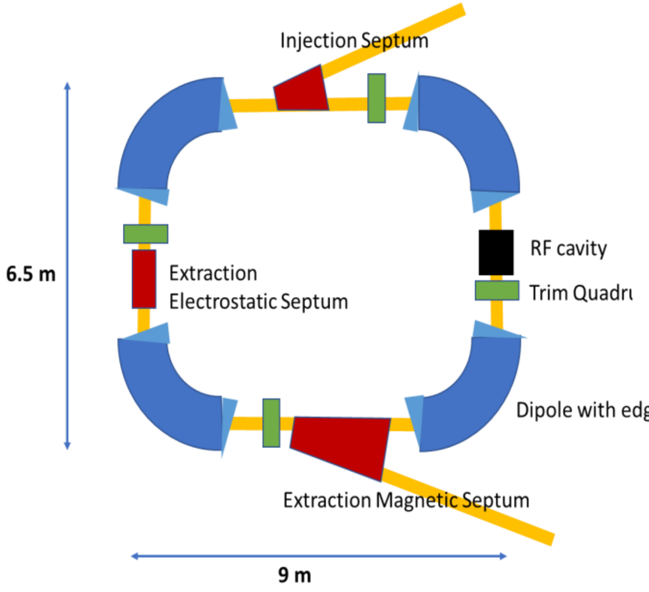
- Modular (can be built in stages)
- Fast energy variation (longitudinal scan of tumour)
- Smaller and less expensive than standard carbon synchrotron

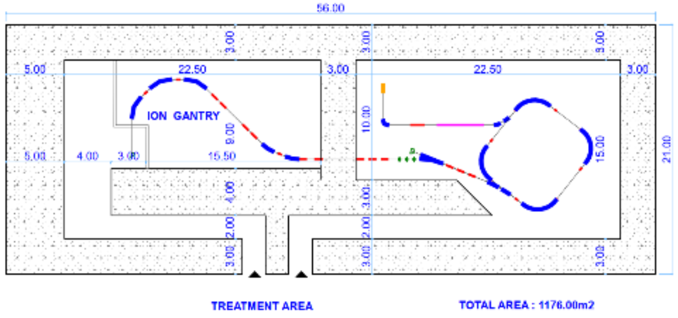
Disadvantages:

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



3. Compact Helium synchrotron





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

NIMMS/HITRI+ has just started the design of a compact Helium synchrotron
(E. Benedetto, SEEIIST/TERA/CERN)

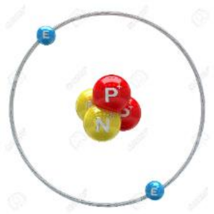
- Use of 3He with higher field in magnets allows keeping similar dimensions as proton synchrotrons
- With 4He the dimensions are 20% larger

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 centre.

Limited R&D required (2T magnets)

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

Could use a dual-mode injector for radioisotopes and accelerate carbon for a penetration of 11 cm (4He)



Advantages:

- Simple and compact, known technologies
- Synchrotron based on standard components
- Can use SIGRUM gantry

Disadvantages:

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

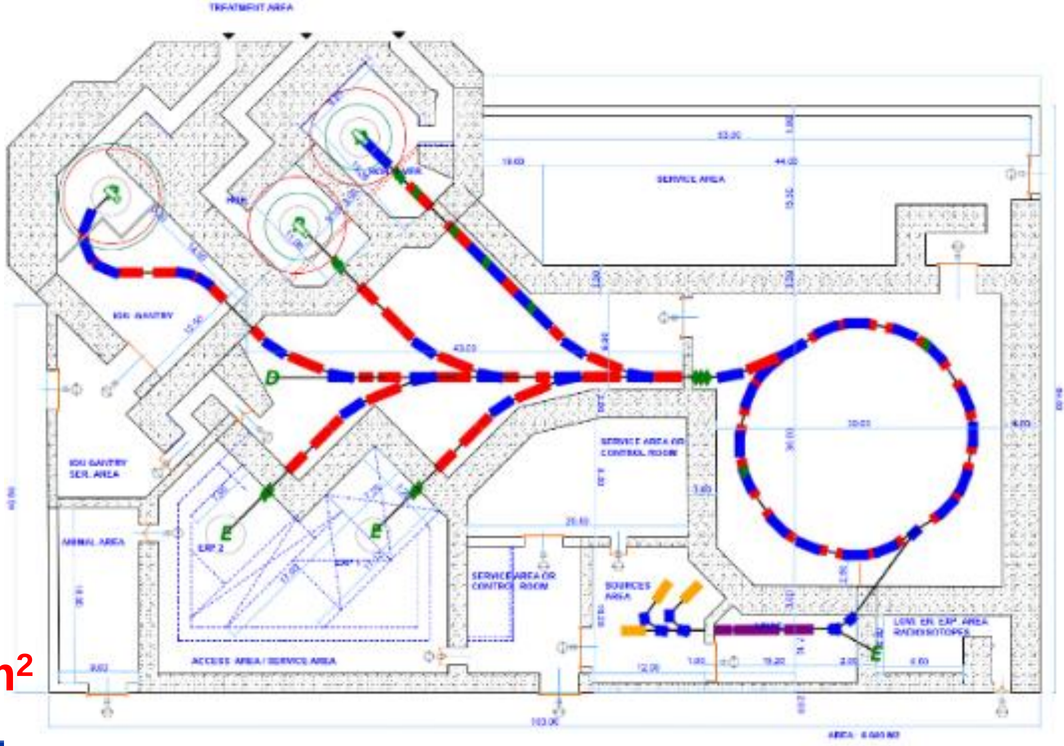
4. Carbon synchrotron (room temp.)

Advantages:
- ➢ Full range of ions: p, He, O, C, Si
- ➢ Synchrotron based on standard components
- ➢ Can use SIGRUM gantry

Disadvantages:
- ➢ No modularity (synchrotron in one go)
- ➢ Cost

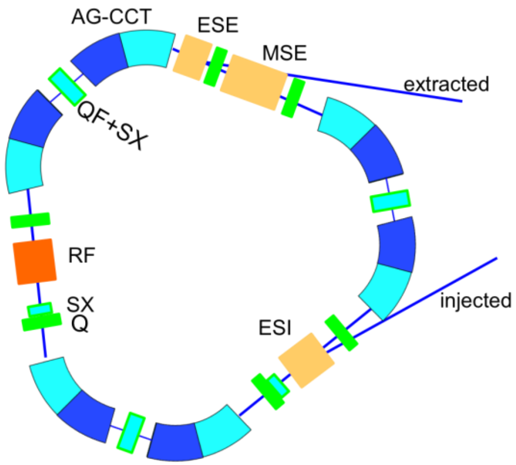
Layout developed for SEEIIST

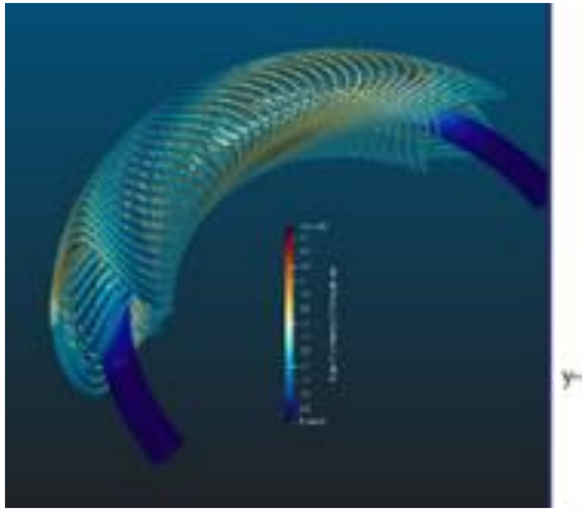
- ➢ Full range of ions (protons, He, O, C, Si,...)
- ➢ Dual-mode injector can produce radioisotopes
- ➢ Optimised for research and treatment
- ➢ Synchrotron based on CNAO and MedA design



Total 6,500 m^2

5. Superconducting Carbon synchrotron





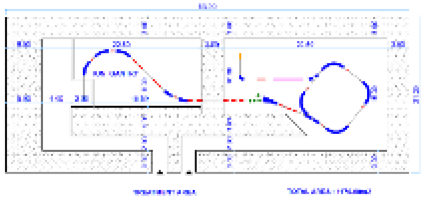
Being developed (magnets and optics) in the HITRI+/IFAST EU projects (E. Benedetto et al.)

Can be used for a compact single room facility or for a SEEIIST-type research and therapy facility.

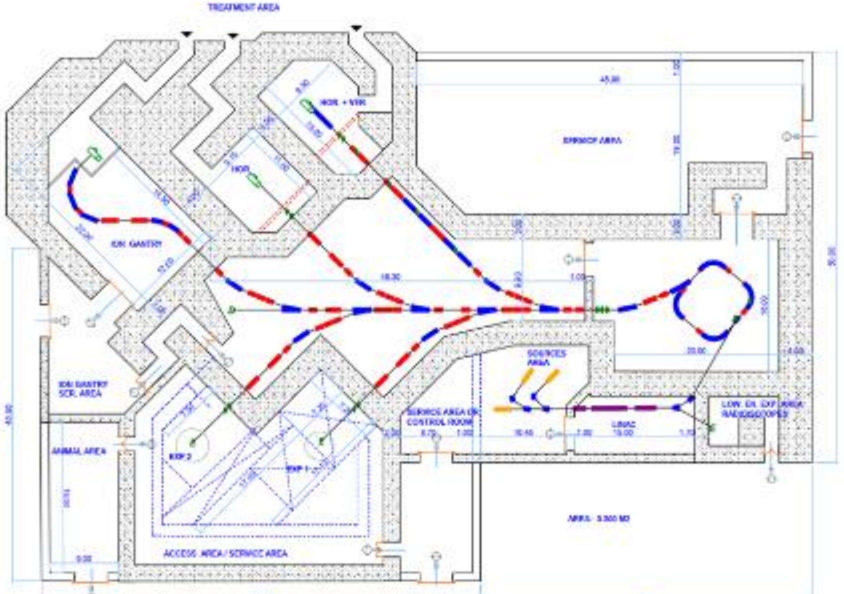
- May use dual-mode injector for radioisotopes
- SC magnets require consistent R&D (3.5 years for demonstrator, 2/3 years more for prototype).

Advantages:
- Wide range of ions: p, He, Ci
- Smaller and less expensive than standard synch.
- Can use SIGRUM gantry
- May include dual-mode linac for isotopes

Disadvantages:
- No modularity (synchrotron in one go)
- Time and risk to develop SC magnets



Single room, 1,000 m2



3+2 rooms, 5,500 m2

Comparison

	Cyclinac	C-linac	He-synchrotron	C-synchrotron (RT)	C-synchrotron (SC)
Particles	p	p, He, C	p, He	p, He, O, C	p, He, C
Dimensions (1)	~400 m^2 (?)	~600 m^2	~600 m^2	~1,200 m^2	~600 m^2
Approx. cost (2)	20	30	20	40	30
R&D needed	medium	high	low	low	high
Risk for R&D	low	medium	low	low	medium
Time to TDR (3)	~1y	~4y	~1.5y	~1.5y	~5y
Radioisotopes	Yes, wide range	no	if needed	yes	if needed
Gantry (4)	no	no	yes (>5y)	yes (>5y)	yes (>5y)
Comm. interest	low	medium	medium	low	high

Note that all these options will need medical licensing before treating patients (cost and time)

(1) Accelerator only – no rooms, without shielding
(2) Accelerator only. Rough estimate in arbitrary units for cost of acc. components
(3) Assuming an expert team working full time; TDR=Technical Design Report
(4) Use of SIGRUM superconducting gantry

Some personal conclusions

- The cyclinac is interesting, but at the end of a long construction process, you have a machine that does exactly what a commercial proton therapy unit does, for a much higher price because of all the medical licensing process. But it can make sense e.g. in the Portuguese environment where they have a running proton centre in Lisbon, and an experimental cyclinac unit in Coimbra.
- The linac is an interesting option, but might take a long time (and a higher than foreseen cost) to develop. ADAM/AVO is building a similar (much easier) linac for protons, started in 2013 with large investments (I have counted some 140 M€ so far), and after 8 years they are far from having a full running prototype. Medical licensing of linacs is a new experience, and no gantry design exists for this type of accelerator. But an advantage is a possible staged approach (build in steps of increasing energy).
- The Helium synchrotron is a nice way to do something new at reasonable cost, risk and construction time. Could be replaced (or integrated) in a second stage with the superconducting carbon synchrotron.
- The room-temperature Carbon synchrotron is the “reference”, construction could be started soon but cost is high and a project should be coordinated with SEEIIST. Risk is low, and no staging is possible.
- The superconducting synchrotron is the most interesting option, also in terms of future commercial use, but requires a long development time with related risks. We can imagine an upgrade path from the Helium synchrotron to the SC carbon one, keeping all the other equipment.

Thank you for your attention

maurizio.vretenar@cern.ch

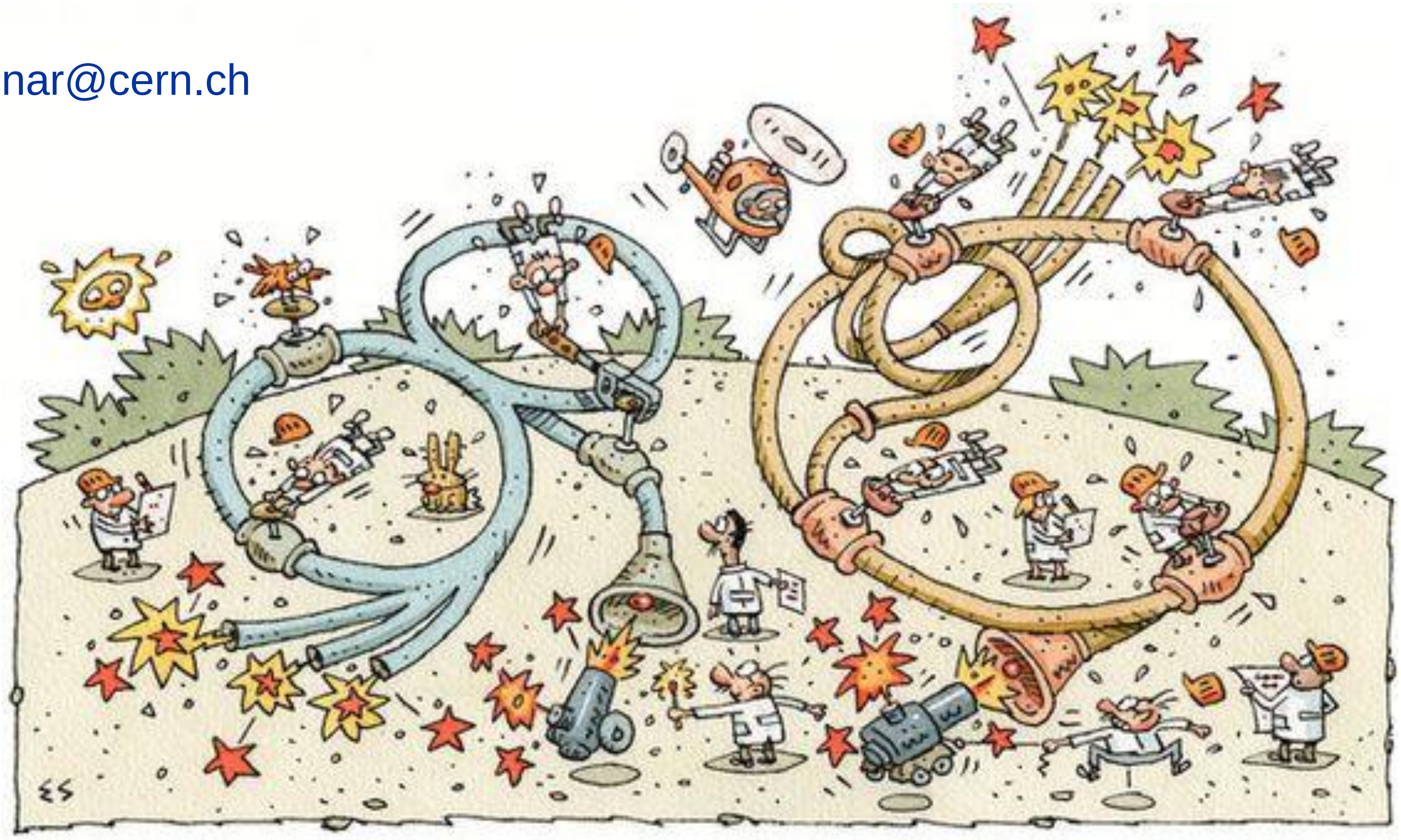


Image credit: Elwood H. Smith, The New York Times