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Next-generation hadron-therapy: Next Ion Medical Machine Study

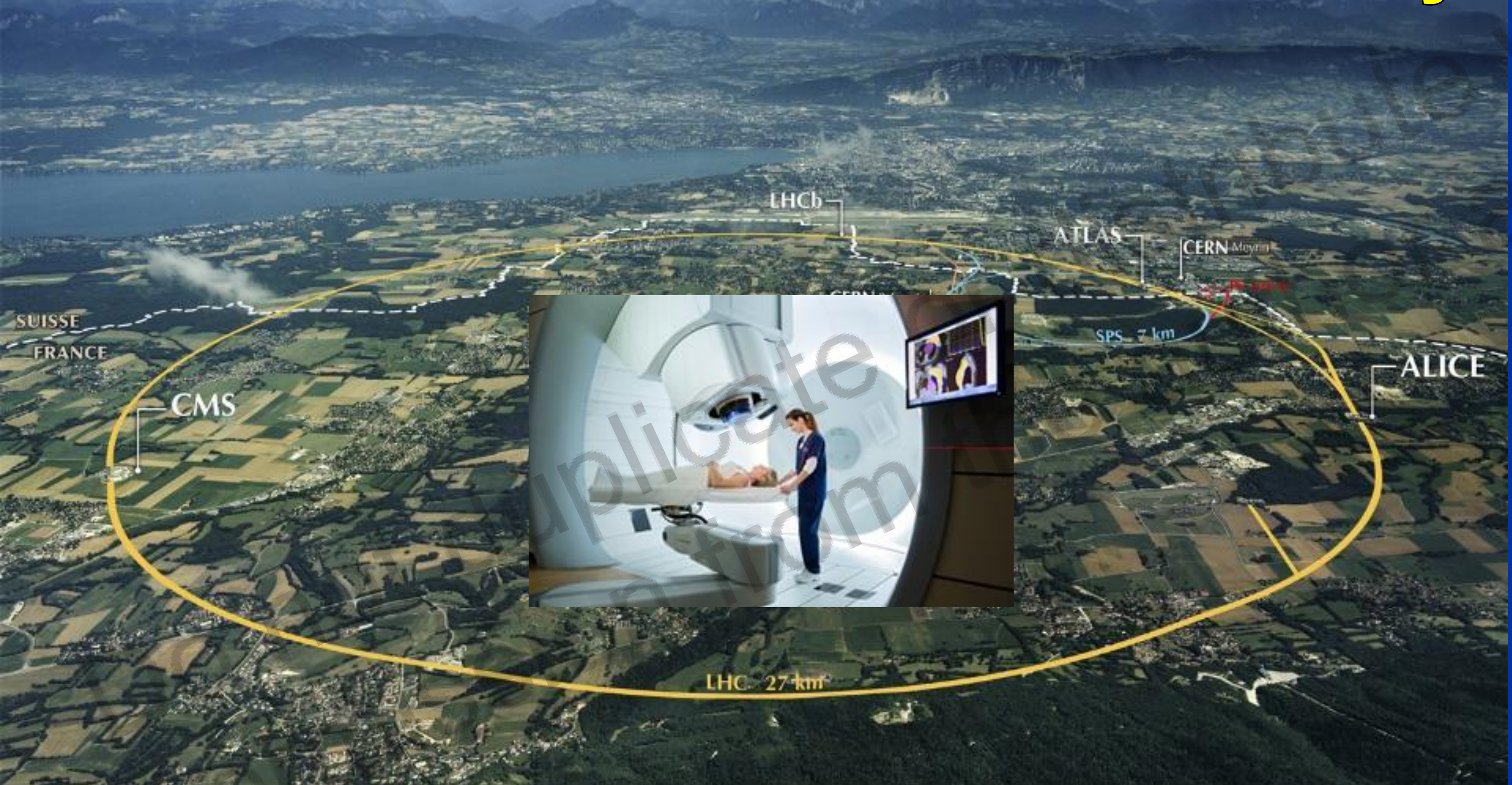
Expert: **Dr Maurizio Vretenar**, CERN, Geneva, Switzerland

Discussant: **Dr Luca Bertolaccini**, European Institute of Oncology, Milan, Italy

Next-generation hadron-therapy: Next Ion Medical Machine Study

Maurizio Vretenar

CERN, ATS/DO
Accelerator and Technology Projects and Studies



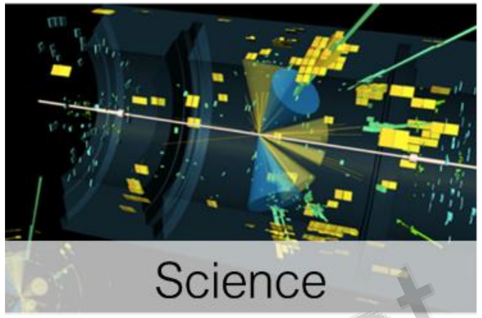
European School of Oncology
e-session 611, 31 March 2022

About CERN

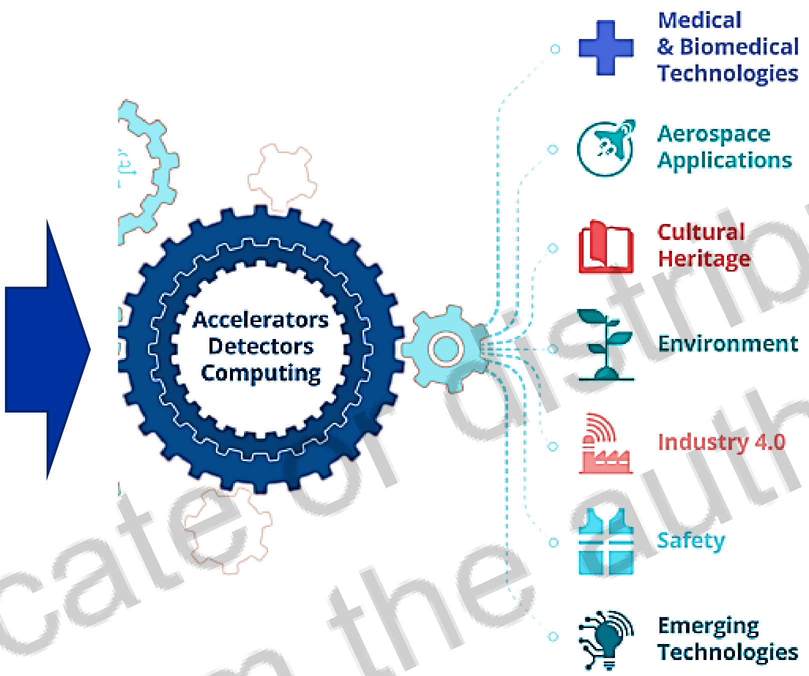
CERN ("Conseil Européen pour la Recherche Nucléaire") was founded in 1954 to promote science for peace.

Today an International Organisation with 23 member states, is the largest particle physics laboratory in the world.

CERN's Mission



From the Large Hadron Collider to medicine

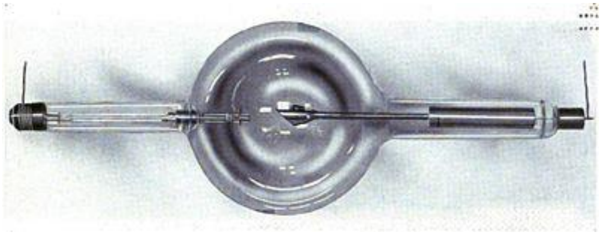


CERN and Society

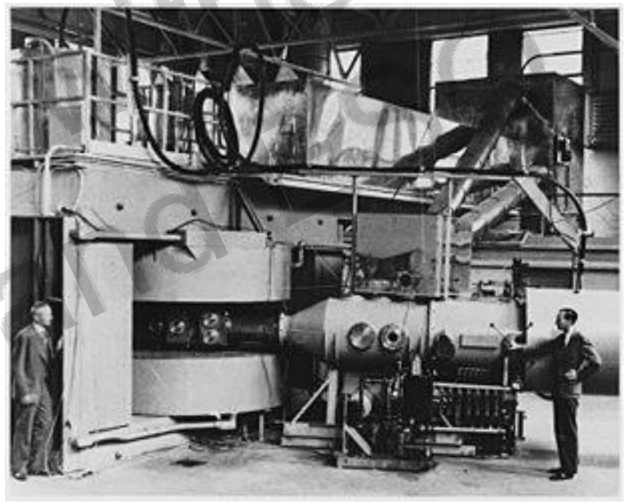
- ➢ Huge experience in all technologies related to acceleration and detection of particles
- ➢ Engaged to maximise the return to society and to demonstrate the impact of major investments as the Large Hadron Collider.

- ❑ MedTech is the main field of application of CERN technologies for the benefit of society.
- ❑ The subatomic world made accessible using particle accelerators can lead to substantial advances in many fields of medicine: treatments with particles, isotopes, advanced diagnostics,…
- ❑ Developing these technologies requires a strong collaboration across physics, biology, medicine - and CERN can provide a fertile collaborative ground for them to grow.

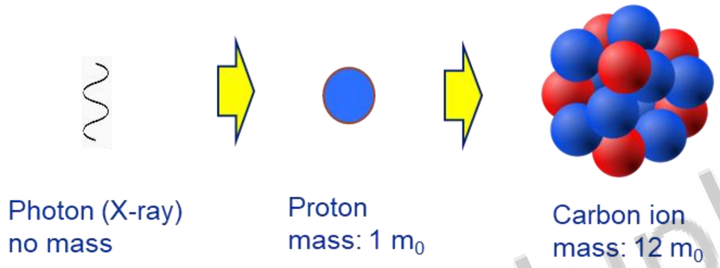
Treating cancer with particle beams



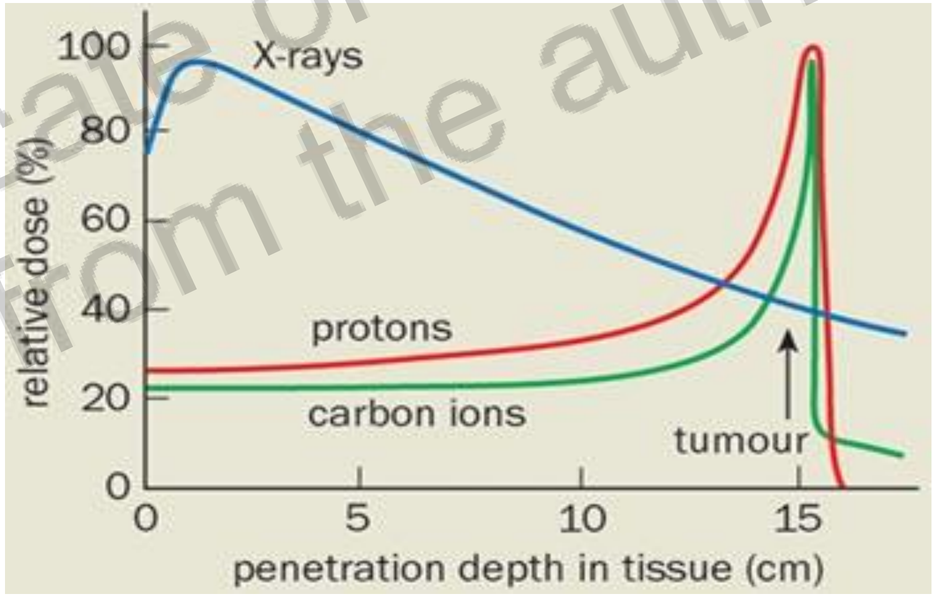
The discovery in 1895 of **X-ray (=photon) sources** has started a new era for imaging in science, industry and medicine.



The invention in 1932 of modern **particle accelerators** has given scientists a new powerful tool to access the subatomic matter and to interact with it.



Different from X-rays, protons and ions (=atomic nuclei) deposit most of their energy at a precise depth inside the tissues, **minimising the dose to the organs close to a tumour**.



accelerators-for-society.org

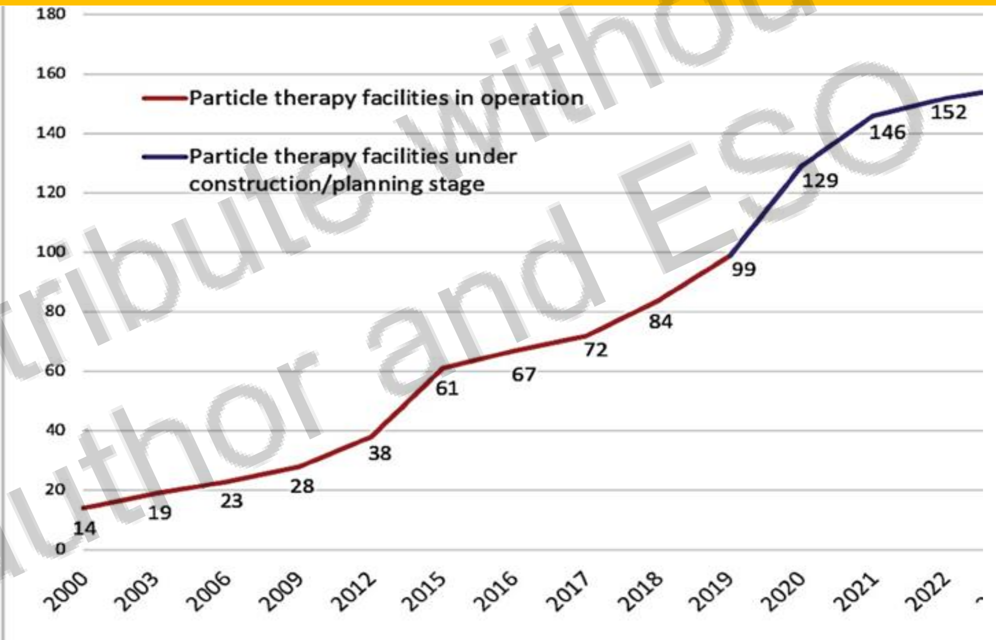
The "**Bragg peak**" is an incredible opportunity to deliver precise amounts of energy at a well-defined position inside the body, sparing adjacent organs *(the ancient dream of bloodless surgery!)*.

The rise of particle therapy (hadrontherapy)

Hadrons = protons and heavier atomic nuclei (ions)

- Proposed 1946, first experimental treatment Berkeley 1954.
- First hospital-based proton treatment facility in 1993 (Loma Linda, US).
- First treatment facility with carbon ions in 1994 (HIMAC, Japan).
- Treatment in Europe at physics facilities from end of '90s.
- First dedicated European facility for proton-carbon ions in 2009 (HIT).
- From 2006, commercial proton therapy accelerators (mostly cyclotrons) come to market.
- In 2022, 6 competing vendors for protons, 1 for carbon ions. A total of 152 centres worldwide.

A success story, but … many ongoing discussions on **effectiveness, costs and benefits**.

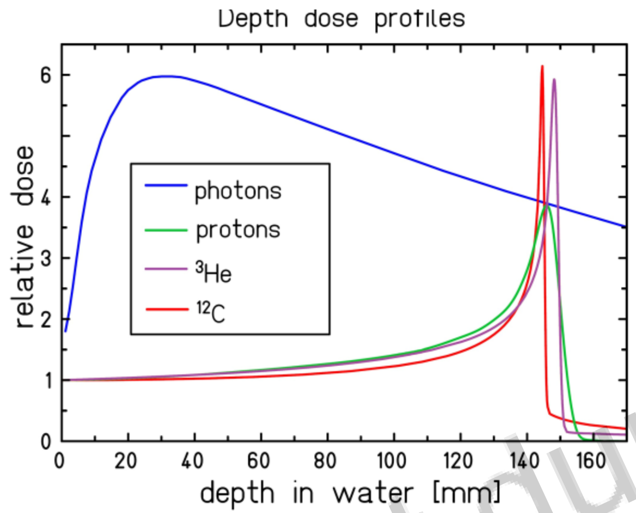


ptcog.com

The Heidelberg Ion Therapy (HIT) facility (protons and carbon ions)

The Bragg peak is not all…

The Bragg peak is very simple physics concept: distribution of energy deposition inside the tissue, leading to *atomic ionisations* (**LET = Linear Energy Transfer**, energy loss per unit mass)



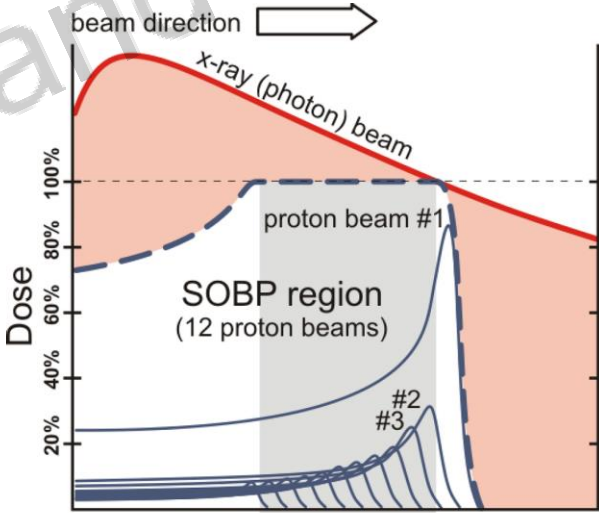
Durante, Debus & Loeffler, *Nat. Rev. Phys.* 2021

Biology is more complex than physics:

- Radiobiological effect **RBE** has a complex dependence on LET and particle type: need of experimental work, complex models and sophisticated treatment plans.

Practical dose delivery reduces effectiveness:

- **Longitudinal** scan of tumour leads to higher dose in the penetration zone (Spread Out Bragg Peak, SOBP),
- The precise dose distribution requires **comparable accuracy** in imaging of tumours and in compensation of organ motion.

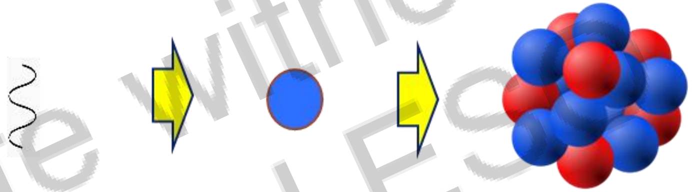


Levin et al., Br J Cancer (2005) 93:849–54

Ion therapy: from photons to protons to ions

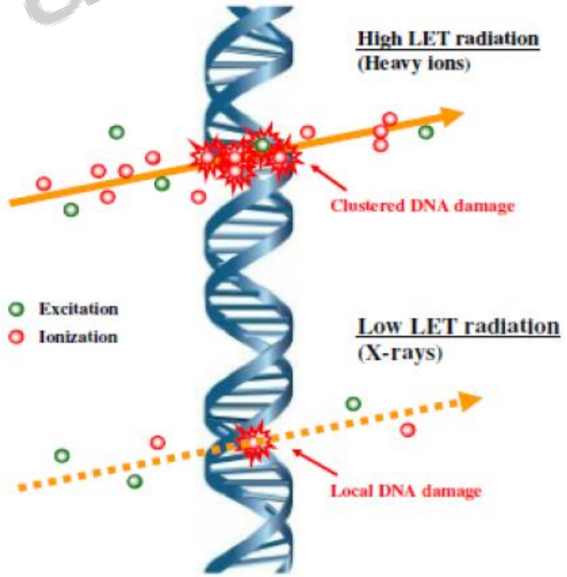
High LET radiation (ions) generates denser ionisations inducing clustered DNA lesions difficult for the cell to repair.

→ **RBE(carbon)=2.0-2.4**



Advantages of heavier ions (compared to protons or X-rays)

- **Higher LET and RBE** generate non-reparable double-strand DNA breakings that are effective on **hypoxic radioresistant tumours**.
- Energy deposition is more precise, with lower straggling and scattering
- Emerging opportunities from combination with immunotherapy to treat diffused cancers and metastasis.



Helm A, Ebner DK, Tinganelli W, Simoniello P, Bisio A, Marchesano V, et al. Combining heavy-ion therapy with immunotherapy: an update on recent developments. Int J Part Ther. (2018) 5:84–93.
Durante M, Formenti S. Harnessing radiation to improve immunotherapy: better with particles? Br J Radiol. (2019) 192:20190224.

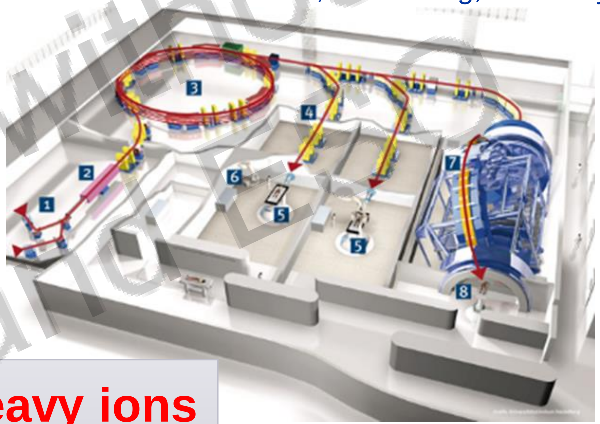
- Only carbon ions licensed for treatment, after the pioneering developments at HIMAC (Japan) from the 90's
- First patient treatments with carbon ions only in 1994: ion therapy is still in an early stage of its development !

And the accelerator?

Ions deliver more energy to the tissues but need more energy to enter the body → factor 2.8 in accelerator diameter going from protons to carbon

Cnao , Pavia, Italy

HIT, Heidelberg, Germany



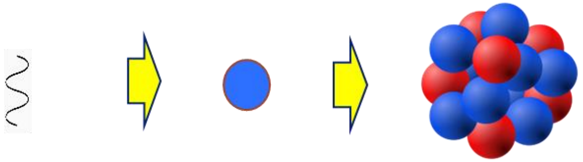
courtesy IBA

Synchrotron, heavy ions
~5,000 m^2
~200 M€

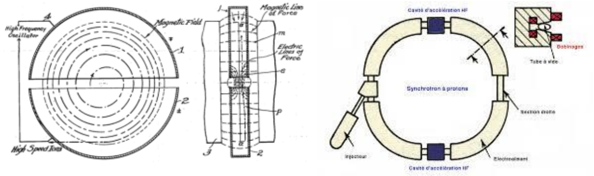
Cyclotron, protons
~500 m^2
~40 M€

Linac, X-rays
~50 m^2
~5 M€

A synchrotron is a "hollow cyclotron": Because higher energies need larger particle orbits, in the synchrotron a time-varying magnetic field covers only the external part.



Wikimedia commons



New technologies for ion therapy accelerators

Ions deliver more energy to the tissues but need more energy to enter the body → the required diameter of the accelerator increases with energy, accelerator dimensions increase by a factor 2.8 going from protons to carbon

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 planned 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.

The ion gantry of the Heidelberg Ion Therapy facility: 600 tons

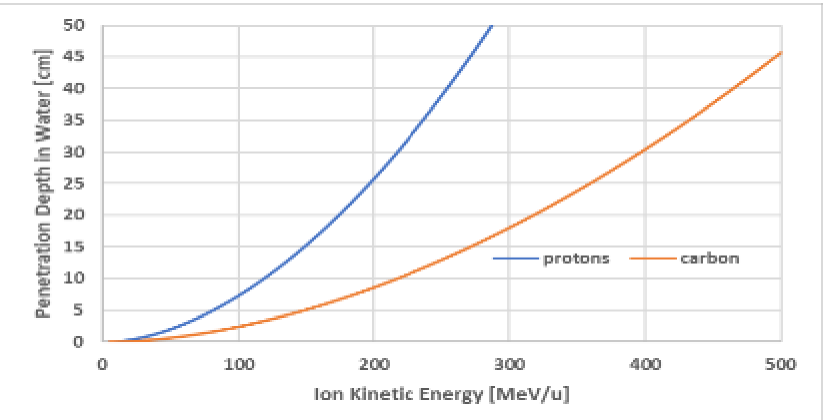
Particle accelerator technology has made a huge progress in the last 20 years, towards more compact and performant accelerator designs.

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

A strategy for CERN

- **Proton** therapy is now commercial, and CERN, as an international organisation, cannot interfere with a mature commercial market.
- **Heavy ion** therapy is still in an early phase despite its advantages. Its diffusion is limited mainly by:
  - ✓ **Size and cost of the accelerator**;
  - ✓ **Lack of experimental data**.
- New demands from the medical community and new opportunities from recent research can be integrated in a newly designed ion therapy facility.

For carbon ions, 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.

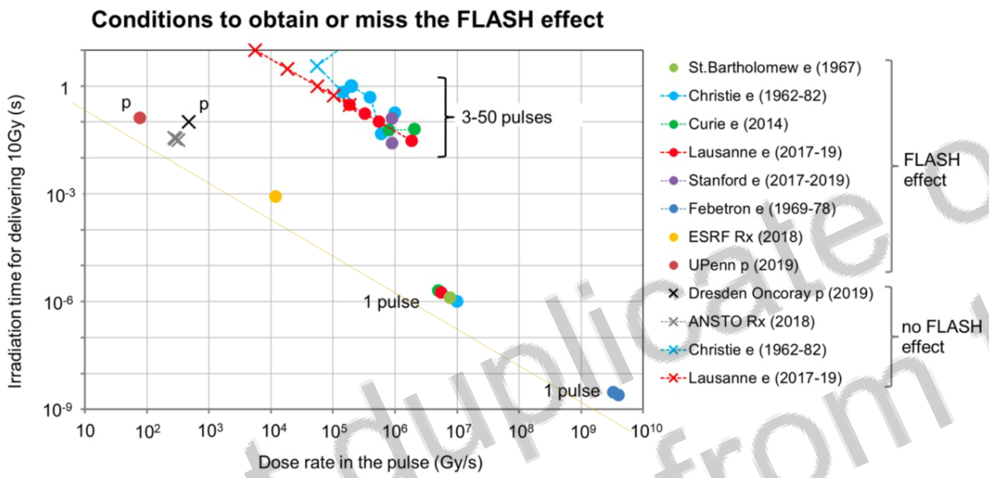


Strong impact on the medical field from an R&D programme based on critical accelerator technologies for a next generation ion therapy and research facility, smaller, possibly less expensive and more performant than the present reference design.

Exploiting new opportunities: FLASH, multi-particles

FLASH radiotherapy

Novel approach using ultra-high dose rate (>40 Gy/s). Early pre-clinical evidence suggests that such dose rates provide significant sparing of healthy tissue compared to conventional radiotherapy without reducing the damage to cancerous cells. **Presently the hottest topic in radiation oncology !**



Montay-Gruel et al. Clin Cancer Res 2020

So far, the technology of proton and ion accelerators limits production of FLASH beams to tests on small volumes.

New accelerator systems are needed for **larger scale experiments and future therapeutic use**.

Multi-ion treatment and imaging

LET-painting in the tumour using different particles from a synchrotron: precise modulation of damage delivery within the most resistant areas, or on-line imaging with ions lighter than the treatment ones. Under development, both techniques present several accelerator challenges

The Next Ion Medical Machine Study (NIMMS)

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.

nimms

Basic requirements of the next generation cancer therapy accelerator:

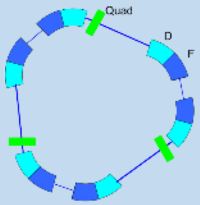
- ❑ Operation with multiple ions: protons, helium, carbon, oxygen, etc. for therapy and research.
- ❑ Lower cost and dimensions, compared to present;
- ❑ Faster dose delivery with higher beam intensity and new delivery schemes (FLASH)
- ❑ A gantry device to precisely deliver the dose to the tumour.

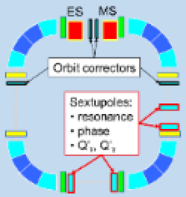
International partners collaborating with NIMMS:

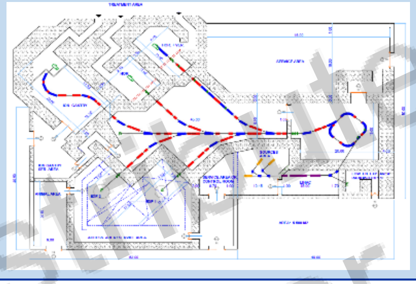
- ❑ SEEIIST (South East European International Institute for Sustainable Technologies)
- ❑ TERA Foundation (Italy)
- ❑ GSI (Germany)
- ❑ INFN (Italy)
- ❑ CIEMAT (Spain)
- ❑ Cockcroft Institute (UK)
- ❑ University of Manchester (UK)
- ❑ CNAO (Italy)
- ❑ Imperial College (UK)
- ❑ MedAustron (Austria)
- ❑ U. Melbourne (Australia)
- ❑ ESS-Bilbao (Spain)
- ❑ Riga Technical University (Latvia)
- ❑ Sarajevo University (Bosnia &H.)

Main research lines for new particle therapy

1. Small synchrotron accelerators (rings)

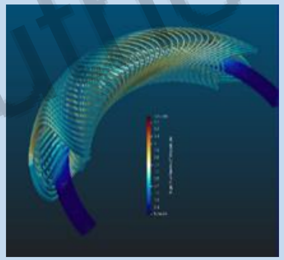






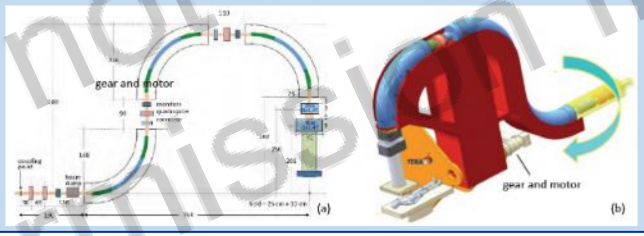
Reduced dimensions with improved performance (injection, extraction)

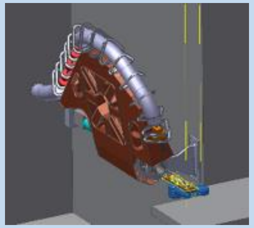
2. Superconducting magnets for small accelerators

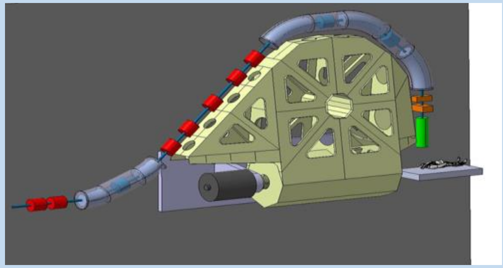


High magnetic fields to bend particles on small orbits

3. Superconducting rotating gantries for ions







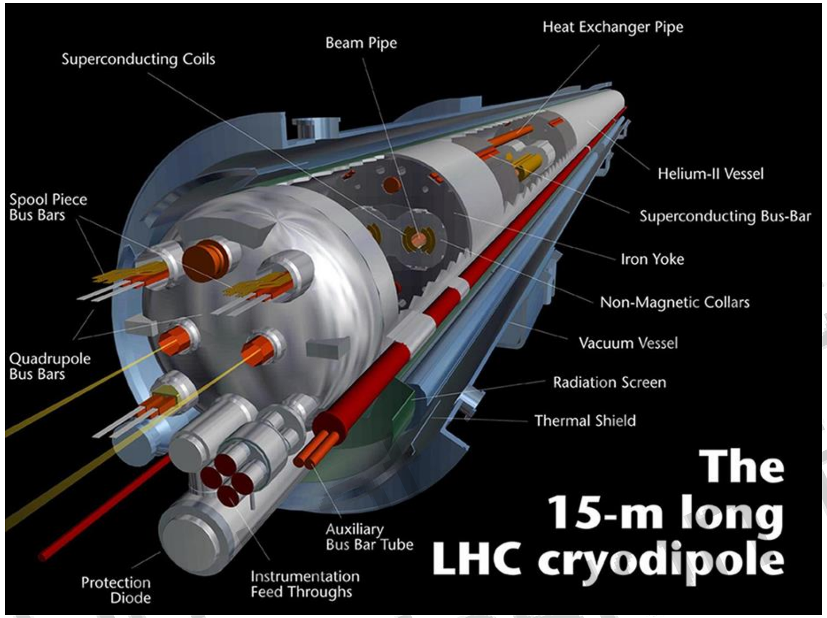
Precise beam delivery on multiple angles

Superconducting magnets for synchrotrons and gantries

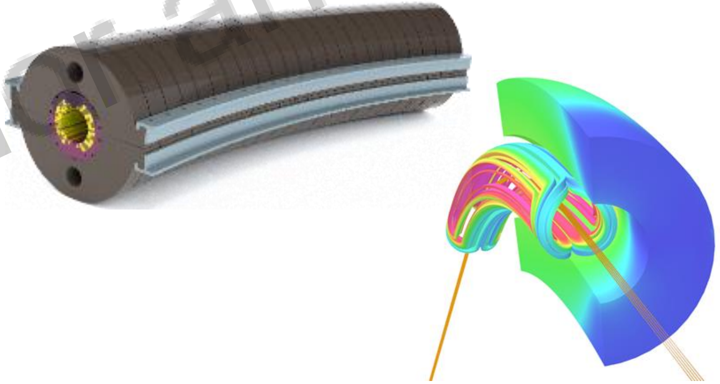
The main avenue to reducing the dimensions of a magnetic system is **superconductivity**.
Here the interest is not (only) in reducing power loss of conductors, but in increasing the magnetic field inside the large magnets that drive the particle beam.

The higher the magnetic field, the smaller the radius of the accelerator!

Medical accelerator magnets have specific challenges: ramping field, curved shape, beam focusing, …



LBNL, USA



CERN (courtesy M. Karppinen)

A new generation of compact superconducting magnets for ion therapy synchrotrons and gantries: 45^0 curvature in 1.3 m, 4 T field

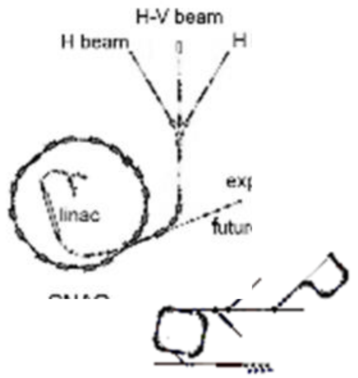
From the huge magnets of the Large Hadron Collider to small sophisticated magnets for therapy synchrotrons

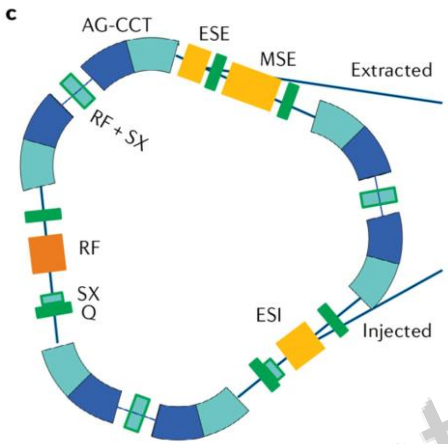
Being developed by a wide collaboration within two EU-funded projects: HITRI+ *(hitriplus.eu)*, I.FAST *(ifast-project.eu).*

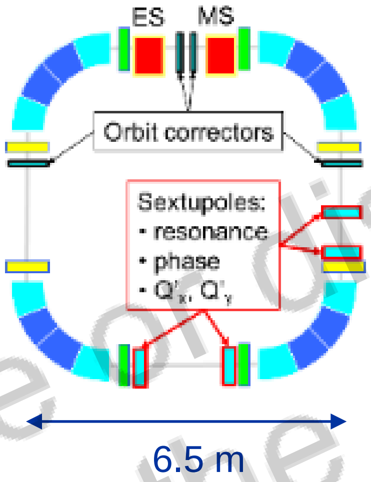
First demonstrator magnets in 3 years

The compact superconducting synchrotron

Considerable gain in dimensions thanks to superconductivity





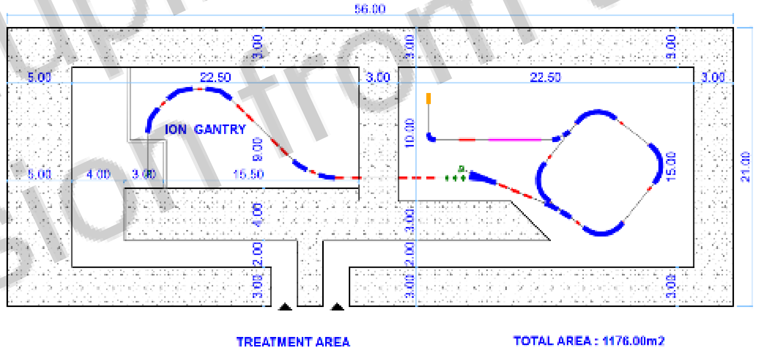


Additional features

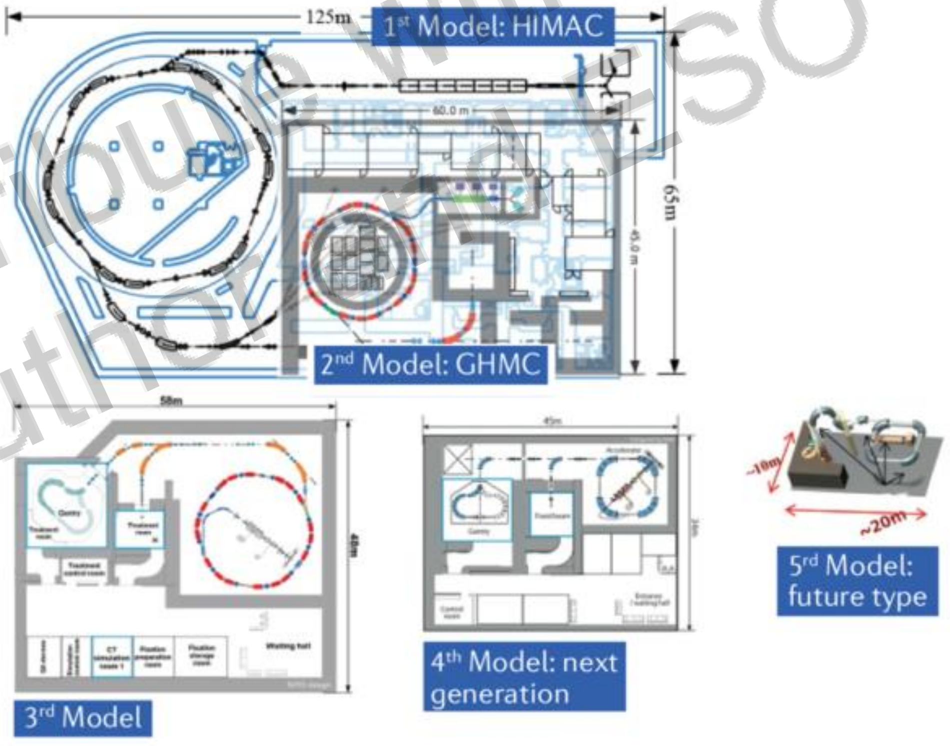
- High intensity (2 x 10^{10} C ions per pulse
- Slow and FLASH extraction
- Multiple ion operation

Goal: a compact single-room ion therapy facility in about 1,000 m²

Alternative synchrotron layouts

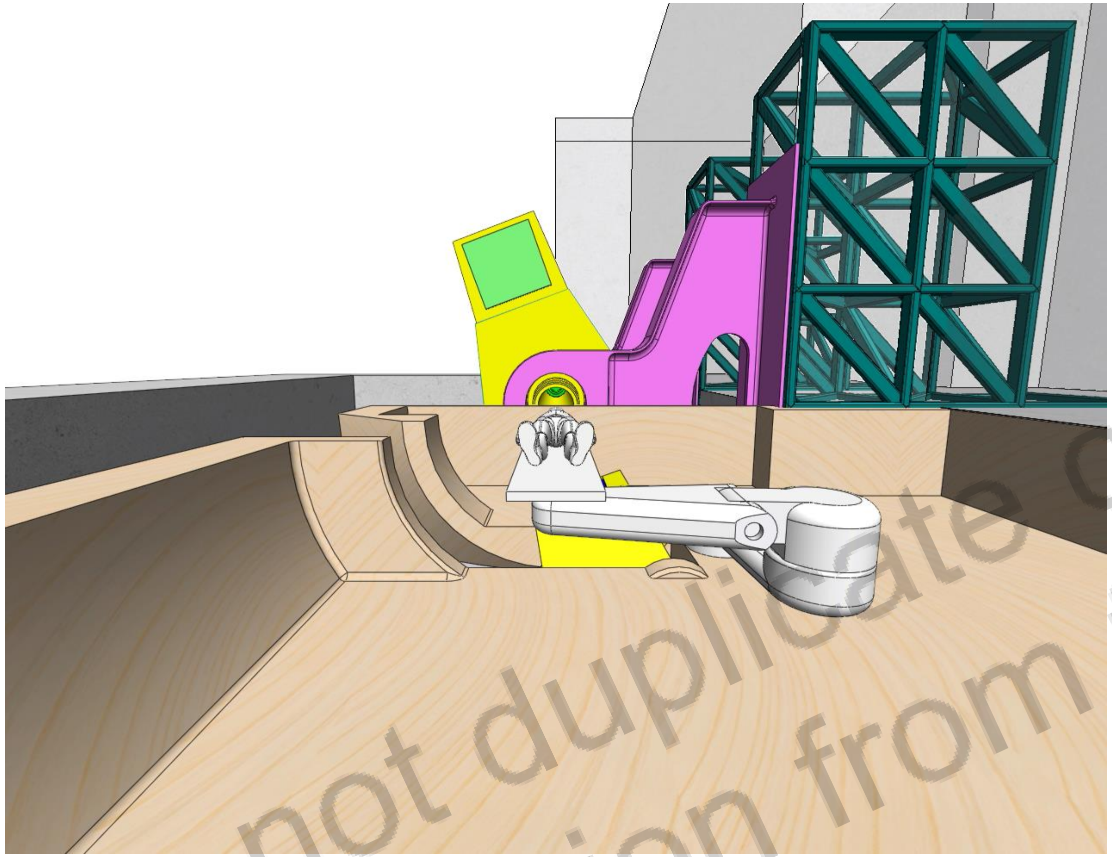


E. Benedetto et al., Comparison of accelerator designs for an ion therapy and research facility, CERN-ACC-NOTE-2020-0068, [*http://cds.cern.ch/record/2748083?ln=en*](http://cds.cern.ch/record/2748083?ln=en)



Japan: the roadmap of the National Institutes for Quantum and Radiological Science and Technology (NIRS-QST, Chiba) for reducing the footprint of heavy ion centres. Form the large HIMAC (1994) to 3rd and next generation (courtesy of K. Noda, NIRS-QST).

An innovative superconducting ion gantry

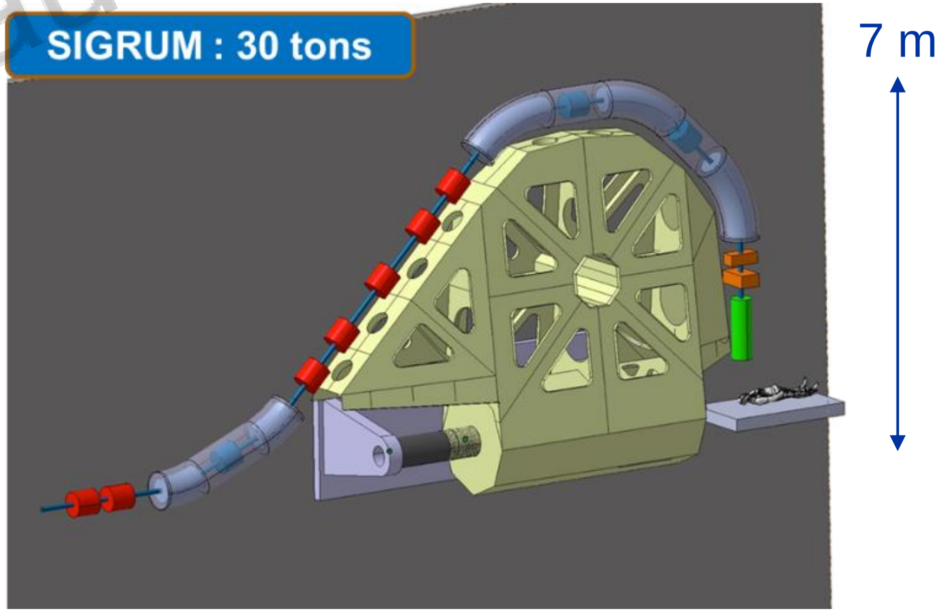


New superconducting magnets and an innovative mechanical design allow for a reduction in weight and size of gantry

Development of a rotating Superconducting Gantry for Carbon ions (SIGRUM), Supported by 2 collaborations:

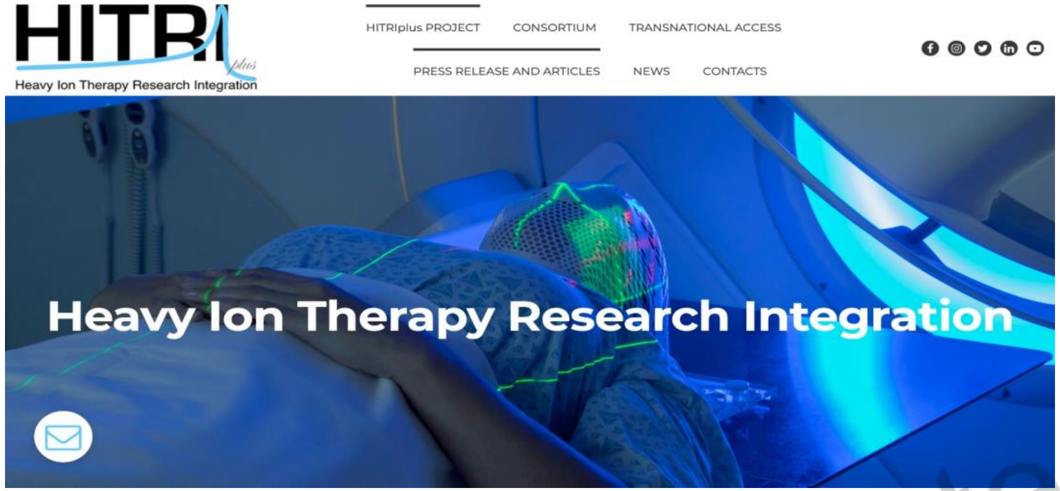
- CERN-INFN-CNAO-MedAustron: magnets, dose delivery, range verification, scanning system.
- HITRIplus EU project (CNAO, RTU, SEEIIST, CERN: optics and mechanics design.

Images courtesy L. Piacentini, RTU/CERN



- *U. Amaldi, N. Alharbi, E. Benedetto, P.L. Riboni, M. Vaziri, D. Aguglia, V.Ferrentino, G. Le Godec, M.Karppinen, D. Perini, E.Ravaioli, D. Tommasini, SIGRUM: A Superconducting Ion Gantry with Riboni's Unconventional Mechanics, CERN-ACC-NOTE-2021-0014, http://cds.cern.ch/record/2766876?ln=en*
- *L. Piacentini, L. Dassa, D. Perini, A. Ratkus, T. Torims, S. Uberti, J. Vilcans, M. Vretenar, Comparative Study on Scenarios for Rotating Gantry Mechanical Structures, CERN-ACC-NOTE-2022-0007, http://cds.cern.ch/record/2802114?ln=en*
- *HITRIplus task 7.5, coordinator M. Pullia (CNAO)*

The HITRIplus EU project



HITRIplus: An Integrating Activity for Starting Communities, (2021-25) supported by the European Commission under the Research Infrastructure Work Programme of Horizon 2020.

18 participants from 14 EU countries, including the 4 operating ion therapy centres, to coordinate and strengthen the EU research programme in ion therapy, developing the instruments for the next generation facilities.

www.hitriplus.eu

The HITRIplus Transnational Access

EC support for teams of scientists to perform research at the 4 ion therapy centres + the GSI ion facility. Two types of access:

Clinical Access, to refer patients to hadrontherapy facilities and share clinical Prospective Investigations and patient follow up, and to allow radiation oncologists to work together in multicentre Prospective comparative studies.

Research Access to perform research activities in the experimental halls of carbon ion facilities and GSI.

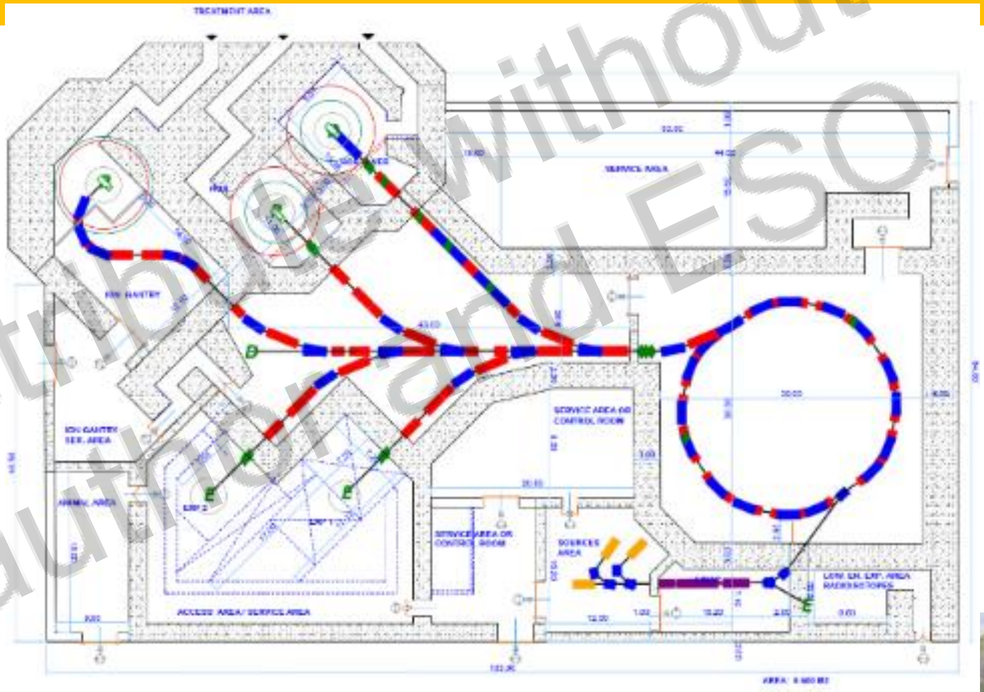
https://www.hitriplus.eu/transnational-access-what-is-ta/

Participant No *	Participant organisation name	Country
1 (Coordinator)	Fondazione Centro Nazionale di Adroterapia Oncologica (CNAO)	IT
2	Bevatech GmbH (BEVA)	DE
3	Commissariat à l'énergie atomique et aux énergies alternatives (CEA)	FR
4	European Organisation for Nuclear Research (CERN)	IEIO
5	Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)	ES
6	Cosylab Laboratorij za kontrolne systeme dd (CSL)	SI
7	GSI Helmholtzzentrum für Schwerionenforschung GmbH (GSI)	DE
8	Universitätsklinikum Heidelberg (UKHD/HIT)	DE
9	Istituto Nazionale di Fisica Nucleare (INFN)	IT
10	EBG MedAustron GmbH (MEDA)	AT
11	Marburger Ionenstrahl-Therapie Betreibergesellschaft mbH (MIT)	DE
12	Paul Scherrer Institut (PSI)	CH
13	South East European International Institute for Sustainable Technologies (SEEIIST)	CH
14	Universita ta Malta (UM)	MT
15	Philipps-University Marburg (UMR)	DE
16	Uppsala University (UU)	SE
17	Wigner Research Centre for Physics (Wigner RCP)	HU
18	Riga Technical University (RTU)	LV

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

The SEEIIST initiative

- **SEEIIST** (South East Europe International Institute for Sustainable Technologies): a new international partnership aiming at the construction of a new Research Infrastructure for cancer research and therapy in South East Europe (11 member countries).
- SEEIIST is supported by the European Commission, to develop the facility design in collaboration with CERN and other partners.
- 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".



Accelerator

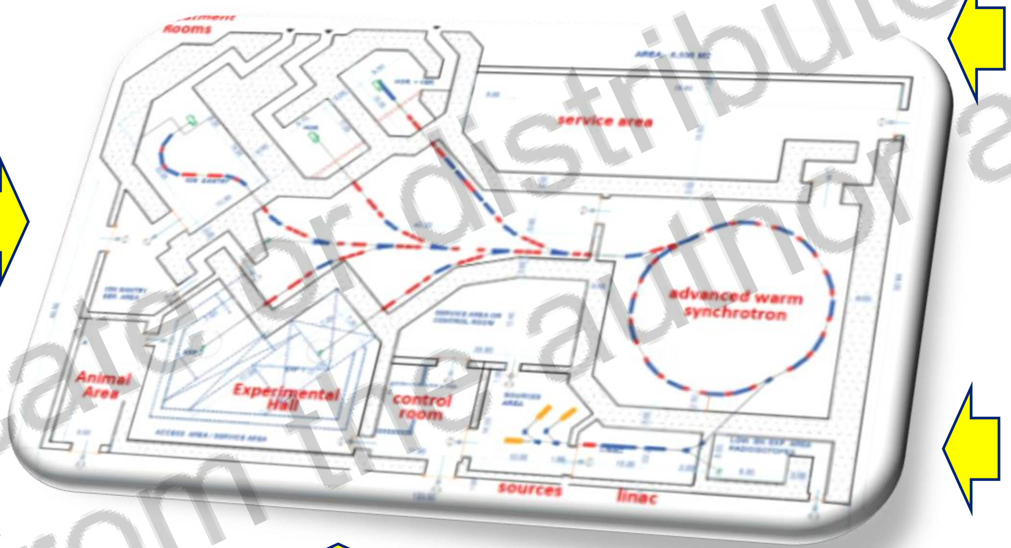
Baseline: conventional normal-conducting synchrotron
Advanced option: superconducting synchrotron

The unique SEEIIST ion therapy and research facility

Intensive design work in 2019/20 in collaboration between CERN and SEEIIST, with the contribution of NIMMS partners and of the main European ion therapy centres

A. Innovative SEEIIST features:

1. Optimised for 50% research and 50% patient treatment (~400 patients/year);
2. Providing 20 times higher beam intensity for carbon ions than present facilities;
3. Equipped with flexible extraction for operation in FLASH mode;
4. Equipped with dual mode linear injector capable of producing radioisotopes for cancer imaging and therapy.



C. Conservative SEEIIST feature:

The synchrotron adopts the well-established PIMMS design (known and available components, flexible layout for research);

D. Specific SEEIIST features:

1. Environmental strategy: minimise energy consumption, strategy for energy generation;
2. Conceived as a multiple-hub facility, to federate partners in different countries.

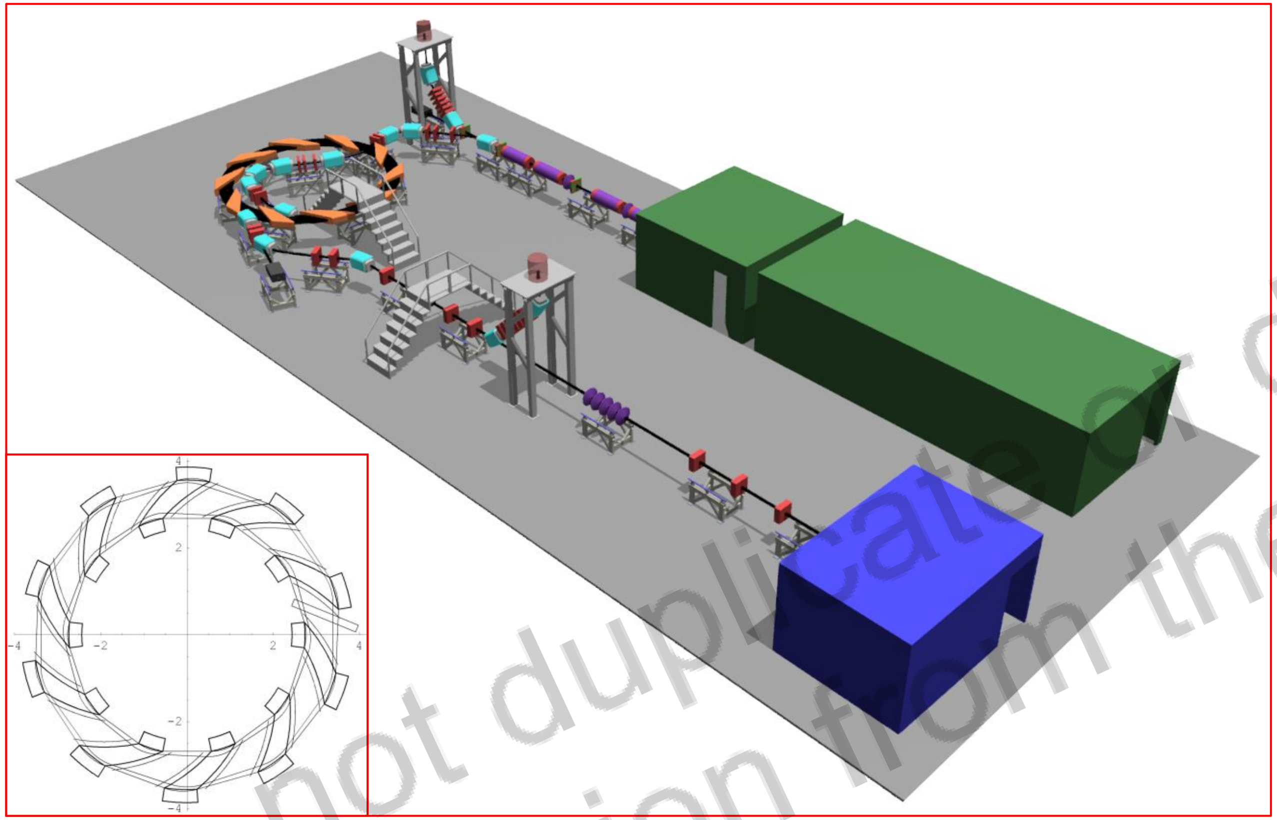
B. Advanced SEEIIST features (common to other advanced facilities):

1. Operation with multiple ions: protons, Helium, Carbon, Oxygen, Argon;
2. Multiple energy extraction for faster treatment;
3. Equipped with a compact superconducting gantry of novel design.

The proposed SEEIIST facility

Roof of accelerator building is removed to show accelerator components

The UK 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

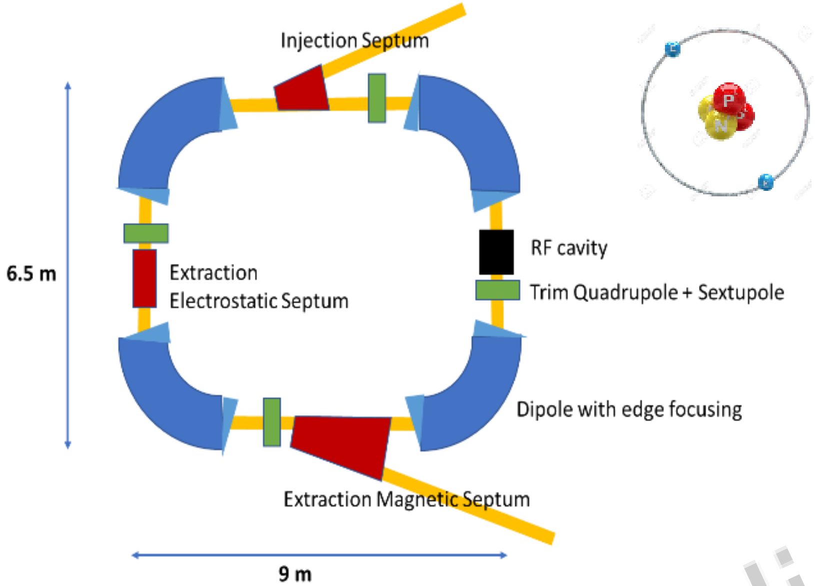
Ion Therapy Research Facility proposal

- 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 new laser-driven source

Collaboration Agreement with NIMMS, is complementary with the NIMMS programme

A compact proton and helium synchrotron



Advantages:

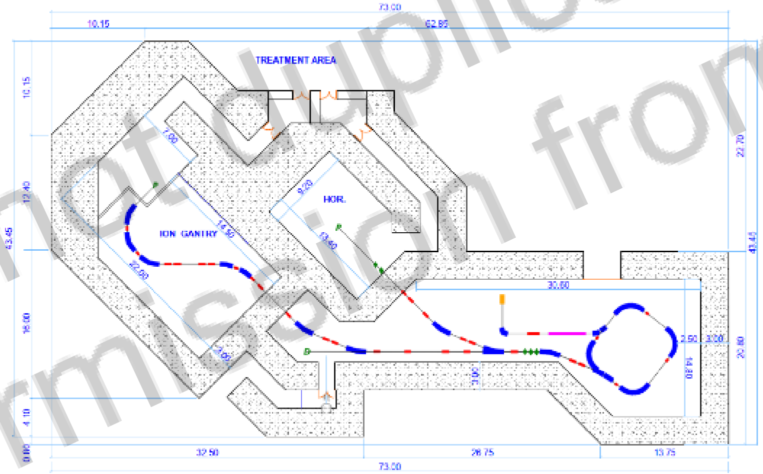
- Simple and compact, known technologies
- Synchrotron based on standard components
- Can use new gantry design

NIMMS has started the design of a Compact Helium Synchrotron

- Operation with protons and helium, high intensity beam with slow and FLASH extraction.
- Option of microbeams and online imaging with protons or prompt gamma.

Helium gives reduced lateral scattering than protons, lower fragmentations than carbon, and with higher RBE than protons could treat some radioresistant tumours at lower cost – wide interest in medical physics community, clinical tests starting at HIT.

Size of the facility: 1,200 m^2 for treatment + about 500 m^2 for research



- Conceptual design ready in 2022.
- Interests from the Baltic scientific community for a new **Advanced Particle Therapy Centre of Baltic States**
- (Estonia, Latvia, Lithuania).

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

Conclusions

Ion therapy is still in its infancy.
Much experimental work and clinical evidence are needed to optimise tools and treatments; its goal is not to replace X-ray (and proton) therapy, but to add to the arsenal of advanced instruments to treat cancer.

The main directions for improvement are:

- Smaller and less expensive accelerators based on the most advanced technologies developed for scientific research;
- Precise online imaging and accurate beam positioning, with compensation for organs in motion;
- Integration of multiple ions and FLASH beams.

Research in accelerators can provide **breakthroughs in particle therapy** (multiple ions, FLASH, medium and high LET beams,…), in conjunction with a robust **experimental programme** in facilities that can devote a large fraction of their time to research.

Physics laboratories like CERN can contribute not only with competencies in physics and technologies, but also acting as aggregation points for wide international and multidisciplinary collaboration.