Hadron therapy accelerators: present and future

*CERN initiatives:* from PIMMS *(Proton-Ion Medical Machine Study)* to NIMMS *(New Ion Medical Machine Study)*

Frédérick Bordry
Director for Accelerators and Technologies
Chair of CERN Medical Applications Steering Committee (CMASC)
CERN: founded in 1954: 12 European States
Science for Peace and Development
Today: 23 Member States

Member States: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Spain, Sweden, Switzerland and United Kingdom

Associate Members in the Pre-Stage to Membership: Cyprus, Slovenia

Associate Member States: India, Lithuania, Pakistan, Turkey, Ukraine

Applications for Membership or Associate Membership: Brazil, Croatia

Observers to Council: Japan, Russia, United States of America; European Union, JINR and UNESCO

~ 2700 staff
~ 1800 other paid personnel
~ 14000 scientific users
Budget (2019) ~ 1200 MCHF
The Mission of CERN

- **Push back** the frontiers of knowledge
  E.g. the secrets of the Big Bang … what was the matter like within the first moments of the Universe’s existence?

- **Develop** new technologies for accelerators and detectors
  Information technology - the Web and the GRID
  Medicine - diagnosis and therapy

- **Train** scientists and engineers of tomorrow

- **Unite** people from different countries and cultures
The goal is to maximise the positive impact of CERN innovations on society, with the help of our partners, through both open and protected dissemination.
Knowledge transfer for the benefit of medical applications

CERN’s core mission is basic research in particle physics.

Transferring CERN’s know-how and technology to other fields, and thus maximising the societal impact of the Laboratory’s research, is an integral part of CERN’s mission.

**CERN’s involvement in medical applications-related activities** and the resulting expectations placed on the Organization by all the relevant stakeholders have been growing over recent years to the point where knowledge transfer for the benefit of medical applications has become an established part of CERN’s programme of activities.
Hadron-therapy Centres

2017: 60 Proton Centres
10 Carbon Ion Centres

Durante M, Orecchia R, Loeffler JS, 2017

Nature Reviews | Clinical Oncology
In Europe, the interest in hadron therapy has been growing rapidly and the first dual ion (carbon and protons) clinical facility in Heidelberg, Germany started treating patients at the end of 2009. Three more such facilities are now in operation: CNAO in Pavia, MIT in Marburg, and MedAustron in Wiener Neustadt are treating patients.

Globally there is a huge momentum in particle therapy, especially treatment with protons (industrial offers).

By 2022 it is expected there will be almost 120 centres around the world, with over 30 of these in Europe.
Number of treated patients with Protons and Carbon-ions

Protons $\sim 80000$

C-ions $\sim 9800$

2017
Protons $\sim 150'000$ (+80%)
C-ions $\sim 22'000$ (+120%)
Other ions $\sim 3'600$
Total $175'600$
Accelerators and their Use

Today: > 30’000 accelerators operational world-wide*

The large majority is used in industry and medicine

- Industrial applications: ~ 20’000*
- Medical applications: ~ 10’000*

Less than a fraction of a percent is used for research and discovery science

- Cyclotrons
- FFAG
- Synchrotrons
- Synchrotron light sources (e-)

* Source: World Scientific Reviews of Accelerator Science and Technology A.W. Chao

* not including CRT televisions…
Accelerator domains

Number of accelerators worldwide

> 30’000*

* not including CRT televisions…

Annual growth is several percent
Sales >3.5 B$/yr
Value of treated good > 50 B$/yr

Medicine is the largest application with more than 1/3 of all accelerators.

<table>
<thead>
<tr>
<th>Medical Applications</th>
<th>45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostics/treatment with X-ray or electrons</td>
<td>44%</td>
</tr>
<tr>
<td>Radioisotope production</td>
<td>1%</td>
</tr>
<tr>
<td>Proton or ion treatment</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Industrial Applications

<table>
<thead>
<tr>
<th>Industrial Applications</th>
<th>&gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion implantation</td>
<td>34%</td>
</tr>
<tr>
<td>Cutting and welding with electron beams</td>
<td>16%</td>
</tr>
<tr>
<td>Polymerization</td>
<td>7%</td>
</tr>
<tr>
<td>Neutron testing</td>
<td>3.5%</td>
</tr>
<tr>
<td>Non destructive testing</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
Radiation therapy nowadays relies mostly on linear accelerators, which in developed countries have replaced the cobalt therapy. Unfortunately many countries with an expected increasing cancer rate are not covered.

~14’000 in operation worldwide!
**Electron Linac** (linear accelerator) for radiotherapy (X-ray treatment of cancer)

- 5 – 25 MeV e-beam
- Tungsten target

**A great example of technology transfer from basic science to society**

**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 transversely 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.

~14’000 in operation worldwide!
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.

Develop a medical linear accelerator that provides **state-of-the-art conventional radiation therapy** in regions where power supply is unreliable, the climate harsh and/or communications poor.
Medical linacs for challenging environments

**November 2016,** Geneva; ICEC Sponsored and CERN hosted Workshop: “Design Characteristics of a Novel Linear Accelerator for Challenging Environments – Improving global access to radiation therapy”

**October 2017,** Geneva; ICEC, CERN, STFC: “Innovative, robust and affordable medical linear accelerators for challenging environments” Outcome: 5 seed corn projects

**March 2018,** Manchester; CERN, ICEC, STFC: “Burying the Complexity: Re-Engineering for the Next Generation of Medical Linear Accelerators for Use in Challenging Environments” Progress on the 5 projects, refine specifications

**March 2019,** Workshop in Gaborone, Botswana with over 60 participants. Attended by oncologists, medical physicists and accelerator experts from 7 African countries, Nepal, ICEC, CERN and UK institutes

1. Local LMIC perspective on healthcare, cancer care, and technology challenges
2. Current radiation therapy systems and challenges
3. Project reports on the STFC funded work packages
4. Education, training and technical support needs
5. Discussion on priorities and next steps

**Radiotherapy at Life Botswana Hospital, Gaborone**
The idea of using accelerators for treating diseases is almost as old as accelerators are:

- 90 years ago in 1928 Rolf Wideröe invents the modern radio-frequency accelerator (for his PhD Thesis at Aachen).
- In 1929 Ernest O. Lawrence in Berkeley adds cyclic acceleration and develops the cyclotron, the first high-energy accelerator, producing 1.1 MeV protons in 1931.

- In 1936, the new Berkeley 37-inch (94 cm) 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 leukaemia and other blood diseases.
Cyclotron

- 1932: 1.2 MeV – 1940: 20 MeV (E.O. Lawrence, M.S. Livingston)
- Constant magnetic field
- Alternating voltage between the two D’s
- Increasing particle orbit radius

- Development lead to the synchro-cyclotron to cope with the relativistic effects.
In 1938 starts **direct irradiation** of patients with **neutrons** from the new 60-inch (152 cm) cyclotron. First direct irradiation of a patient, 20 Nov. 1939 (from left: Dr. R. Stone, J. Lawrence, patient R. Penny) in a special treatment room on the new 60-inch cyclotron.

**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.**

In 1946, Robert Wilson proposed to use protons to treat cancer, profiting of the Bragg peak to deliver a precise dose to the tumour (*Wilson had been working at Berkeley, then moved to Harvard and finally founded Fermilab*).

First treatment of pituitary tumours took place at Berkeley in 1956.

First hospital-based proton treatment centre at Loma Linda (US) in 1990.

**Courtesy Maurizio Vretenar**
The Bragg peak is a pronounced peak on the Bragg curve which plots the energy loss of ionizing radiation during its travel through matter. For protons, α-rays, and other ion rays, the peak occurs immediately before the particles come to rest.

When a fast charged particle moves through matter, it ionizes atoms of the material and deposits a dose along its path. A peak occurs because the interaction cross section increases as the charged particle's energy decreases.

For protons and other ions the peak of energy loss occurs just before the particles reach a halt.
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 energies:
- Protons: 60 – 250 MeV/u
- Carbons: 120 – 430 MeV/u

Beam energy accuracy: 0.25 MeV/u
Protons and Carbons: $\sim 10^{10}$ per pulse
• 1946, Robert Wilson proposed to use protons to treat cancer, profiting of the Bragg peak
• 1954 first experimental treatment in Berkeley.
• 1956 treatment of pituitary tumours in Berkeley
• 1958 first use of protons as a neurosurgical tool in Sweden
• 1974 large-field fractionated proton treatments program begins at HCL, Cambridge, MA
• 1990 first hospital-based proton treatment facility (Loma Linda, US).
• 1994 first treatment facility with carbon ions in 1994 (HIMAC, Japan).

From end of ‘90s, treatments in Europe at physics facilities.
• 2009 first dedicated European facility for proton-carbon ions (Heidelberg).
• From 2006, commercial proton therapy cyclotrons appear on the market (but Siemens gets out of proton/carbon synchrotrons market in 2011).
• Nowadays 4 competing vendors for cyclotrons, one for synchrotrons (all protons).

A success story, but … increasing investment and operation cost, still large footprint,…
At present, the cyclotron is the industrial accelerator to provide proton therapy reliably and at “lower cost” (4 vendors on the market).
Quirónsalud Proton Therapy Center, located in Madrid, is a modern center equipped with cutting edge medical technology to offer the highest quality and precision treatment.

It will be a space for innovation and research and it will contribute to the improvement of the results of cancer treatments and the quality of life of patients.

IBA Proteus ONE includes the latest generation Pencil Beam Scanning, isocenter volumetric imaging as well as the Philips Ambient Experience. This machine reduces the acceleration weight and energy consumption by a factor of four.

Largest user community of the world: 34 IBA-equipped proton therapy centres are in operation today around the world.

Capacity of 800 patients/year. (400 patients/year initially)

First level of medical staff composed of experts of national and international prestige with great background in proton therapy in international centers in France, Netherlands or Switzerland.

First patient treatment in Spain with proton therapy in Spain: December 26, 2019
IBA Proteus ONE, Cyclotron

- Most compact design ever developed → Easy to install, integrate, operate and finance.
- Sub-millimetric precision → Compact gantry 360° with its 220° rotating structure combined with the 6 degrees of freedom of movement of Robotic Patient Positioner.
- First flash radiotherapy technic in the only compact image-guided IMPT solution. → high dose of radiation at an ultra-high dose rate.
- Compact image guided solution → Stereoscopic X-ray imaging and Cone Beam Computed Tomography CBCT at isocenter for patient position verification and anatomical modification assessment.
- Latest Pencil Beam Scanning → Minimum radiation exposure to healthy tissue.
- Possibility to upgrade the facility with PT modules.
At present, the cyclotron is the industrial accelerator to provide proton therapy reliably and at “lower 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
3. Ion therapy: cyclotrons cannot be easily used because of the dimensions and complexity (needs superconductivity) and because of the complexity of ion extraction from cyclotrons.

All existing ion medical accelerators are large synchrotrons.
Hadron therapy accelerators: present and future
Frédérick Bordry
Fundacion Aceres, Madrid, 11th February 2020

1943: Mark Oliphant described his synchrotron invention in a memo to the UK Atomic Energy directorate

**Synchrotrons**

- Fixed radius for particle orbit
- Varying magnetic field and radio frequency
- Important focusing of particle beams (Courant – Snyder)

- 1959: CERN-PS and BNL-AGS
- Providing beam for fixed target physics
- Light sources as ALBA
- Paved the way to colliders
CERN accelerators
LHC: an accelerator of 27 km
Proton Therapy Unit

- First In-Hospital Proton Therapy Unit at a Cancer Centre in Spain
- Being part of the Universidad de Navarra, it is a non-profit academic institution with two distinctive features in its DNA: research and knowledge transfer
- Integrating state-of-the-art technology: the first Hitachi synchrotron in Europe, present in American and Japanese hospitals internationally renowned for cancer treatment
- Integrated in a Hospital and the Cancer Centre Universidad de Navarra:
  - Access to the most advanced cancer therapies
  - Designing a personalised treatment with all available precision therapies
  - Clinical trials and competitively funded research projects (national and international bids)
  - Legacy of having led the implementation of the most advanced radiotherapy techniques
- A team of renowned professionals with proven care and research experience, trained at the world’s most specialised facilities in proton therapy and synchrotron technology
• 360° rotation \(\rightarrow\) Irradiation from any angle
• 30 x 40 cm² Maximum field
• Cone Beam CT \(\rightarrow\) Reduces uncertainty in patient preparation
• Pencil Beam Scanning \(\rightarrow\) Greater dose accuracy and less damage to healthy tissue

• “Real-time tumour tracking” based on orthogonal fluoroscopy images \(\rightarrow\) tumour motion
• No subsequent beam degradation process required
• “Multi energy extraction system” \(\rightarrow\) reduces the patient’s irradiation time
• Two-gantry expandable system
Ion therapy accelerators: synchrotrons

- 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.
The Proton Ion Medical Machine Study (PIMMS) was hosted at CERN at the end of the 1990s and supported by MedAustron, Onkologie-2000 and the TERA Foundation. Outcome: synchrotron design optimised for treating cancer with protons and carbon ions (a toolkit!).

Design further adapted by TERA and finally evolved into CNAO (Italy), with seminal contributions from INFN. MedAustron (Austria) was built starting from the CNAO design.
~20 years later (and after the LHC construction!):

next generation of ion therapy accelerators?

A new collaborative study to develop the design and the key components for a new generation of medical accelerators:

- more compact
- cost-effective
- light-ion (carbon, helium,...)
Workshop 19-21 June 2018: jointly organised by CERN, the European Scientific Institute (ESI) and GSI
https://indico.cern.ch/event/682210/overview

~60 experts from all over the world

Requirements from the particle therapy community and initial set of medical specifications

**Accelerator**

- Lower cost, compared to present (~120-150 M€);
- Higher beam intensities than present ($10^{10}$ ppp);
- Reduced footprint, to about 1’000 m$^2$;
- Lower running costs.

**Delivery**

- Fast dose delivery (possibly with 3D feedback);
- Equipped with a rotating gantry;
- Using multiple ions;
- With range calibration and diagnostics online.
Two possible designs for the future facility:
- **Superconducting Synchrotron**
- **Linear Accelerator**

1. Injector linac (10 MeV)
2. Superconducting synchrotron
3. Folded linac
4. Beam delivery and gantry

**Compare and analyse different options**

Jan 2019- Jun 2020

**Technical design study and prototyping of the selected accelerator configuration**

Jul 2020 – June 2022
Options for next generation ion therapy

**Superconducting synchrotron**
CCT-type magnets, Bmax 3.5T,
Ring 27m

**Linear accelerator**
Folded, 53m length,
high rep. frequency and intensity,
low emittance

Size comparison:
Superconducting (top left)
vs. CNAO (bottom left)
and Medaustron (right)

**Superconducting gantry**
Two options being analysed:
- Rotational CCT magnets (TERA)
- Toroidal (L. Bottura, CERN)
The TERA Foundation launched and directed by U. Amaldi is promoting accelerators for cancer therapy since 1992. It has launched in 1995 a collaboration with CERN for the development of a proton therapy linac operating at high frequency (3 GHz) and high gradient (30-50 MV/m) reaching 230 MeV in 25 meters.

The development is now continued by ADAM (an AVO company).
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 Linac4 RFQ Radio Frequency Quadrupole (the first element of any ion acceleration chain) at high frequency – targeted at low current applications requiring small dimensions, low cost, low radiation emissions, up to portability.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Energy</th>
<th>Length</th>
<th>Gradient</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linac4 RFQ</td>
<td>352 MHz</td>
<td>3 MeV</td>
<td>3 m</td>
<td>1 MeV/m</td>
</tr>
<tr>
<td>HF-RFQ</td>
<td>750 MHz</td>
<td>5 MeV</td>
<td>2 m</td>
<td>2.5 MeV/m</td>
</tr>
</tbody>
</table>

Fabrication cost per meter about 50% for HF-RFQ.

The prototype unit (5 MeV protons) has been built at the CERN Workshops and is now used in front of the LIGHT prototype linac of ADAM.
A CERN Collaboration with Spanish Partners is being seting out, arisen from the need of fostering the development of state-of-the-art accelerator technologies providing the most promising irradiation techniques in a cost-effective way by using linear accelerators.

This collaboration aims at facing the first accelerator stage of a carbon ion therapy LINAC: the development of a fully operating and cost-effective injector for $^{12}$C$^{6+}$. It will cover the production of $^{12}$C$^{6+}$ ions in an ion source, based on the MEDeGUN design developed by CERN, their extraction and injection to a novel high frequency RFQ and a final acceleration with a low beta cavity. The auxiliary systems required for a full operational facility will also be provided. After the commissioning phase, the developed prototypes as well the whole injector will be integrated in Spanish premises.

The development of this injector will involve industrial partners in the different phases of the project, covering engineering design, manufacturing issues, commissioning of the different components and support on its lay out.

In convergence with the European initiatives (NIMMS, SEEIIST HITRI)
Ion extraction line
vacuum chambers
machining of internal mechanical parts
UHV and bakeable

5-6 T horizontal superconducting magnet
bore diameter 20 cm
solenoid length 150 cm
with or without cryo-cooler
dry or wet system

High-compression electron gun
high-precision machining
braze challenges
UHV and bakeable
GaToroid: A Novel Superconducting Compact and Lightweight Gantry for Hadron Therapy

Luca Bottura
TE-MSC, CERN

22 November 16:00 Council Chamber
Join us for coffee at 15:30

https://indico.cern.ch/e/gantry
GaToroid: A Novel Superconducting Compact and Lightweight Gantry for Hadron Therapy

**Protons**
Torus dimensions: ~1.5 m x 3 m
Estimated mass: 12 tons

**Carbon ions**
Torus dimensions: ~3 m x 5 m
Estimated mass: 50 tons
CERN is collaborating with the SEEIIST (South East Europe International Institute for Sustainable Technologies), a new international partnership aiming at the construction of a particle therapy facility in South East Europe.

SEEIIST has received a preliminary funding of 1 M€ from the EC, part of which will be used to finance 2 FTEs working on ion therapy accelerator design for the next 18 months under the supervision of CERN (18pm for beam optics, 6pm for diagnostics and extraction + 6pm for magnet design).

EU Design Study proposal to the last call of H2020 Research Infrastructures, was submitted in November 2019, mobilising some 15-20 partners. 3 years duration 2020/23, 3 MEUR, co-funded. Heavy Ion Therapy Research Infrastructure Design Study Proposal (HITRI)

The Design Study with: CERN, GSI, CEA, U. Liverpool, INFN, CNAO, Medaustion, HIT, IAP, Cosylab, U. Melbourne + SEEIIST and other partners in the region.

Other partners interested in collaborating with CERN are from India, Latvia, Iran, Spain, Sweden, etc.

A dedicated collaboration for the design of a superconducting gantry, possibly of the toroidal type, has been started with CNAO, INFN and MedAustron.
Medical accelerators is a vast and promising field, connected to accelerator, detector and computing technology drivers. There is wide space for improvement and for exciting new developments. Proton therapy is rapidly progressing, thanks to the commercial availability of turnkey facilities.

There is indication that ion therapy has a strong potential (effective with radio-resistant tumours) but population some action is needed along three axis:

- To reduce size and cost of the facility, using superconducting synchrotron accelerators and/or linear accelerators.
- To collect more data from biomedical research with different types of ions (tissues, tests on animals and possibly clinical trials). Dedicated research beam lines are indispensable.
- Alternative ions are being considered and are essential.
- To optimise the delivery system, including gantry superconducting development.

Conclusions
“There is no applied science if there is no science to apply”
Bernardo Houssay, Nobel Laureate in Medicine (1947).

"The task of the mind is to produce future"
Paul Valéry

Muchas gracias por su atención.