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CNAO: beginnings, status and upgrades¹

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Abstract – The history of the Italian National Centre for Oncological Hadrontherapy (CNAO) spans over thirty years and is fundamentally rooted in the initial concept proposed by Professor Ugo Amaldi when, in May 1991, he co-published the seminal report “*For a Teletherapy Centre with Hadrons*”, marking the definitive start of hadron therapy initiatives in Italy. Later on, in 1992, he founded TERA, the non-profit Foundation that was essential for the scientific and technical development of the project over three decades. Amaldi’s work team was instrumental in the PIMMS (Proton and Ion Medical Machine Study) collaboration at CERN, which generated the optimized PIMMS/ TERA design. By the end of 2003, TERA formally transferred the extensive technical and intellectual property to the CNAO Foundation. CNAO, officially established in 2000 and operating since 2011, is universally recognized as one of the only eight multi-ion centres in the world. It has treated over 5700 patients by mid-2025, specializing in complex and radio-resistant tumour treatments using both protons and carbon ions. The centre is now developing with the CNAO 2.0 expansion, which incorporates a new Proton *Gantry*, the AISHa (Advanced Ion Source for Hadrontherapy) multi-ion source and a new BNCT (Boron Neutron Capture Therapy) facility. Amaldi’s scientific breadth also initiated the Compact Accelerators Programme, leading to the successful development and testing of the LIBO (Linac BOoster) prototype. The successful story of CNAO and TERA continues to be guided by Ugo Amaldi’s distinctive values of “profound intellectual mastery” and “remarkable attention to people”. Finally, Amaldi promoted the creation of the Swiss TERA-CARE Foundation in August 2023, with the aim of focusing on novel synchrotrons and implementing radiotherapy in developing and low-income Countries.

Keywords: Hadrontherapy, Protons, Carbon Ions, Accelerators

Riassunto – La storia del Centro Nazionale di Adroterapia Oncologica (CNAO) si estende per oltre trent’anni ed è fondamentalmente radicata nel concetto iniziale proposto dal Professor Ugo Amaldi, quando, nel maggio del 1991, Amaldi ha co-pubblicato il rapporto fondamentale intitolato “*Per un Centro di Teleterapia con Adroni*”, segnando l’inizio definitivo dell’adroterapia in Italia. Successivamente, nel 1992, ha fondato TERA, la Fondazione che è stata essenziale per lo sviluppo scientifico e tecnico del progetto nell’arco di tre decenni. Il gruppo di lavoro di Amaldi è stato determinante nella collaborazione PIMMS (Proton and Ion Medical Machine Study) presso il CERN, che ha generato il progetto ottimizzato PIMMS/TERA. Entro la fine del 2003, TERA ha formalmente trasferito l’ampia proprietà intellettuale e tecnica alla Fondazione

¹ This peer reviewed article originates from contributions to the “Symposium for Ugo’s 90 years” held at CERN (Geneva) on the 4th of April 2025 to celebrate the 90th birthday of Ugo Amaldi, member of the Accademia dei XL since 1992.

CNAO. Il CNAO, istituito ufficialmente nel 2000 e operativo dal 2011, è riconosciuto universalmente come uno dei soli otto centri multi-ione al mondo. A metà del 2025, ha trattato oltre 5700 pazienti, specializzandosi in tumori complessi e radiore-sistenti per mezzo dell'utilizzazione sia di protoni che di ioni carbonio. Il centro si sta ora sviluppando con l'espansione CNAO 2.0, che incorpora un nuovo *Gantry* a protoni, la sorgente multi-ione AISHa (Advanced Ion Source for Hadron-therapy) e una nuova struttura BNCT (Boron Neutron Capture Therapy). L'ampiezza della visione scientifica di Amaldi ha anche dato il via al Programma Acceleratori Compatti, che ha portato allo sviluppo e al collaudo del prototipo LIBO (*Linac Booster*). La storia di successo di CNAO e TERA continua ad essere guidata dai valori distintivi di Ugo Amaldi caratterizzati da "profonda padronanza intellettuale" e "notevole attenzione alle persone". Infine, nell'agosto 2023, Amaldi ha promosso la creazione della Fondazione Svizzera TERA-CARE, con l'obiettivo di concentrarsi su nuovi sincrotroni e sull'implementazione della radioterapia nei Paesi in via di sviluppo e a basso reddito.

Parole chiave: Adroterapia, Protoni, Ioni Carbonio, Acceleratori

Introduction

In May 1991 – when in Geneva he was coordinating nearly five hundred physicists for the realization and use of DELPHI, one of the four large experiments of the LEP (Large Electron-Positron Collider) accelerator – Professor Ugo Amaldi published, together with Professor Giampiero Tosi, at the time, director of Medical Physics at the Niguarda Hospital and Italy's best-known medical physicist, the report titled "*Per un Centro di teleterapia con Adroni*" (*For a teletherapy centre with hadrons*) (Fig. 1). This article marks the beginning of hadron therapy in Italy.

Sandro Rossi graduated in Physics in November '89 at the University of Milan, with an experimental thesis on the electromagnetic calorimeter called *High density Projection Chamber* (HPC), in the group of Professor

Antonino Pullia. The HPC was one of the detectors that make up the LEP experiment called DELPHI and directed by Amaldi. Rossi first met Amaldi one evening in the summer of 1988 in the well of the DELPHI experiment. Rossi, "with a wrench in his hand and smeared with grease", was asked by the *big boss* himself: "Who are you and what are you working on?" When Rossi replied that he was a student from Milan and was in Geneva for his thesis work, Amaldi invited him to make an appointment in his office at CERN to discuss in detail the work in progress. A few days later, while waiting in the antechamber, the emotion of being in the *big boss's* office, with a constant coming and going of people who had appointments with him, became excitement when he saw his father Edoardo Amaldi, one of the legendary "boys from Via Panisperna", enter, urgently needing to speak with his son. Yet Ugo Amaldi found time to devote to the student and, besides reading drafts of the thesis, he also gave him useful advice.

This was the first approach of the author with Professor Ugo Amaldi. A man with a remarkable attention to people and values first, and then a profound intellectual mastery across an extraordinary range of disciplines – from the technical precision of accelerators and detectors and the fundamental principles of physics and science, to the philosophical depths of theology and societal implications – demonstrated by an astounding portfolio of over 350 published papers (Fig. 2) on top of about 300 physics research papers.

The history of the project for the establishment of the Italian National Centre for Oncological Hadrontherapy (CNAO) spans over more than three decades, from the initial scientific concept in 1991 to the new technologies that are close to start activities.

1. 1992-1995: The origins and the Novara Project

The CNAO initiative began in 1991, when Ugo Amaldi and Giampiero Tosi proposed the first Italian research and development project in hadrontherapy in their report *Per un Centro di teleterapia con adroni* (Fig. 1). The project's fundamental objective was the introduction of external radiotherapy techniques using hadrons (such as protons and carbon ions) for tumour treatment in Italy.

In September 1992, the TERA Foundation (*TERapia con Radiazioni Adroniche*), a non-profit moral entity, was established in Novara. TERA was founded because the National Institute for Nuclear Physics (INFN) had made it clear that it would not employ full-time person-



Fig. 1. The first report dealing with a centre of hadrontherapy in Italy. First of a long series of TERA Reports.

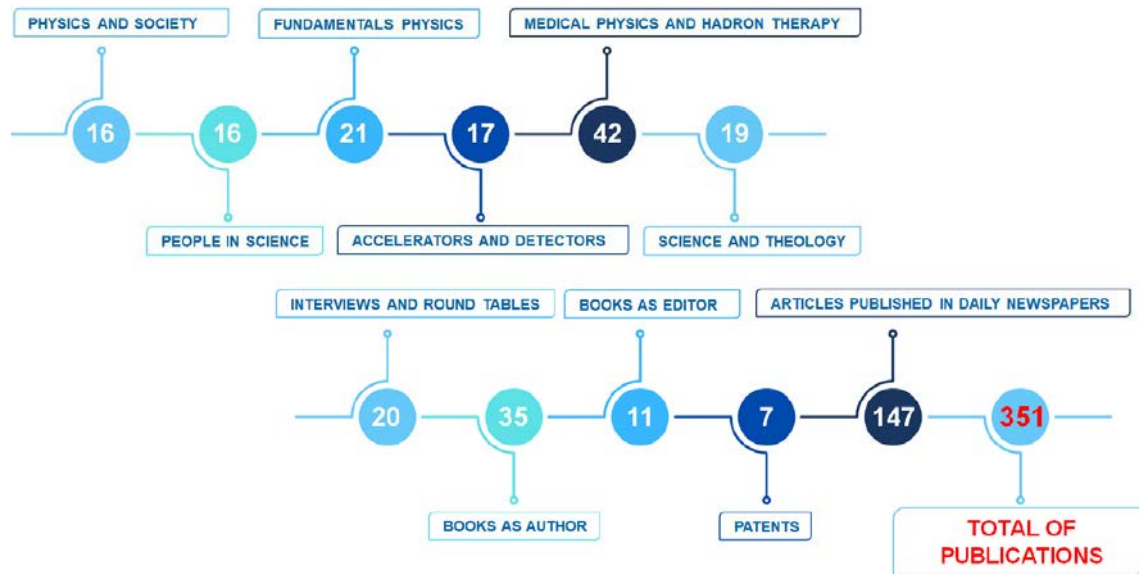


Fig. 2. Ugo Amaldi's publications from 1958 to 2018. Scientific research papers are not included.

nel dedicated to this specific activity. In more than thirty years of activities, the TERA Foundation enrolled more than 250 employees and fellows working at the different projects. TERA received formal recognition from the Ministry of Health in 1994. Initial R&D activities were financially supported by INFN through the ATER (AdroTERapia) experiment.

Between 1992 and 1995, TERA primarily focused on the design of a centre capable of accelerating particles up to 400 MeV/u. The resulting comprehensive design, intended for the Ospedale Maggiore della Carità in Novara, was based on a synchrotron optimized for protons and light ions. This project was documented in the “Blue Book” (1995) [1].

In December 1995, the project gained crucial institutional support when the Italian National Oncological Commission approved the positive report produced by the Study Group chaired by Professor Umberto Veronesi. This report indicated that approximately 300-400 Italian patients per year had elective indications for proton-therapy, with up to an additional 1,000 patients benefiting from the modality. Despite this endorsement, the Novara project was eventually shelved, due to changes in the local political landscape and hospital management.

2. 1996-2002: Reorganization, Mirasole, and the PIMMS/TERA Design

Following the difficulties encountered in Novara, a new Promoter Committee for the CNAO was constitut-

ed in 1996. It included TERA, five large IRCCS hospitals in Milan and Pavia, the Polytechnic of Milan, and the Universities of Milan and Pavia. The Committee chose the site near the Mirasole Abbey in Opera, south of Milan, and drafted the Statute for the “Fondazione Medico Scientifica Mirasole”, intended to construct and manage the CNAO, relying on TERA for technical and scientific input [2]. In 1997, this project, described in the “Red Book”, was stopped by the Health Minister, who did not approve the participation of the four public IRCCS hospitals.

In parallel, TERA was instrumental in launching the PIMMS (Proton Ion Medical Machine Study) collaboration at CERN between 1996 and 2000, contributing 25 man-years to the effort. PIMMS focused on designing a synchrotron and optimized beam lines for light ion therapy, specifically carbon ions and protons (Fig. 3) [3].

Between 1999 and 2002, TERA produced the “PIMMS/TERA” design, modifying and improving the original PIMMS layout to create a more compact and flexible facility (Fig. 4). TERA bore alone the full task of the design refinement and political advancement of the project from 1998 to 2001.

The defining breakthrough occurred in 2000, when the recently nominated Health Minister Umberto Veronesi officially established the CNAO Foundation. After a change in government, the Minister Girolamo Sirchia confirmed the initial funding in November 2001, following the positive review of an ad-hoc Committee and the Board of CNAO was established; it counted

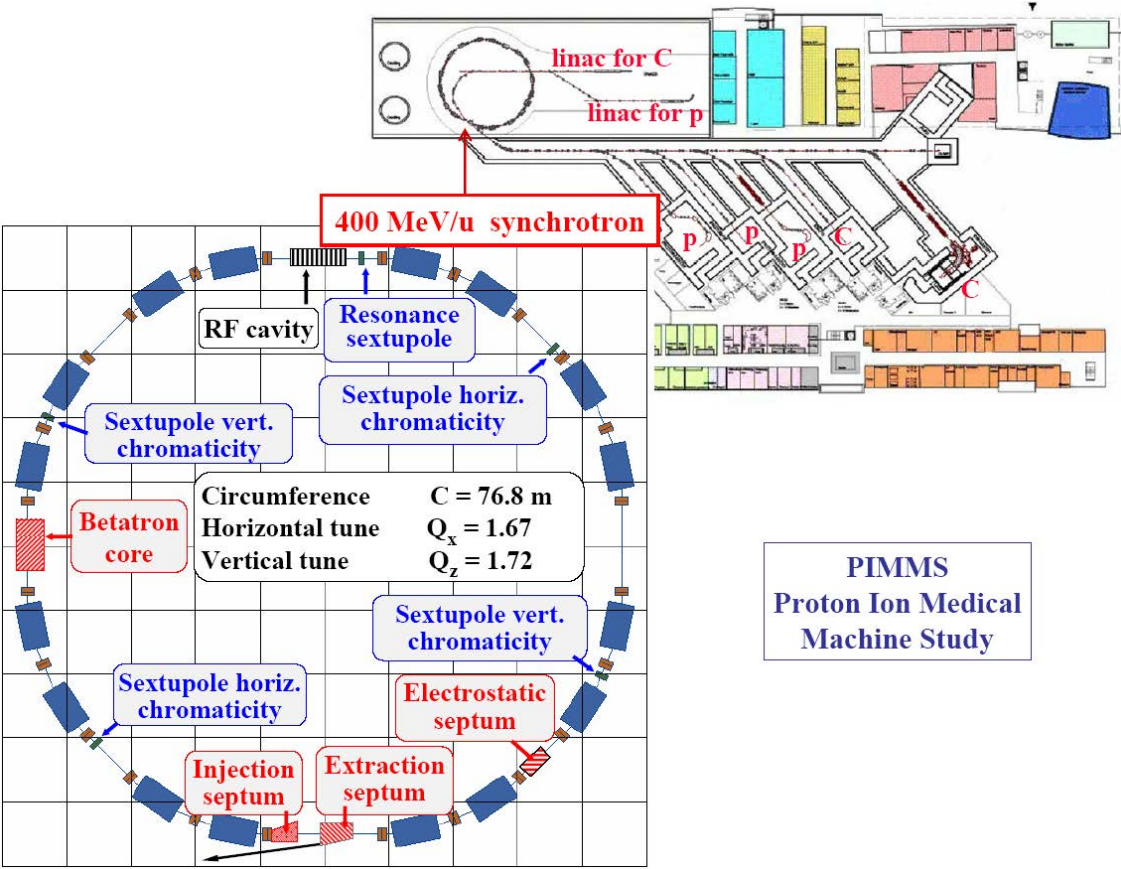


Fig. 3. The layout of the centre designed by the PIMMS group and details of the synchrotron lattice.

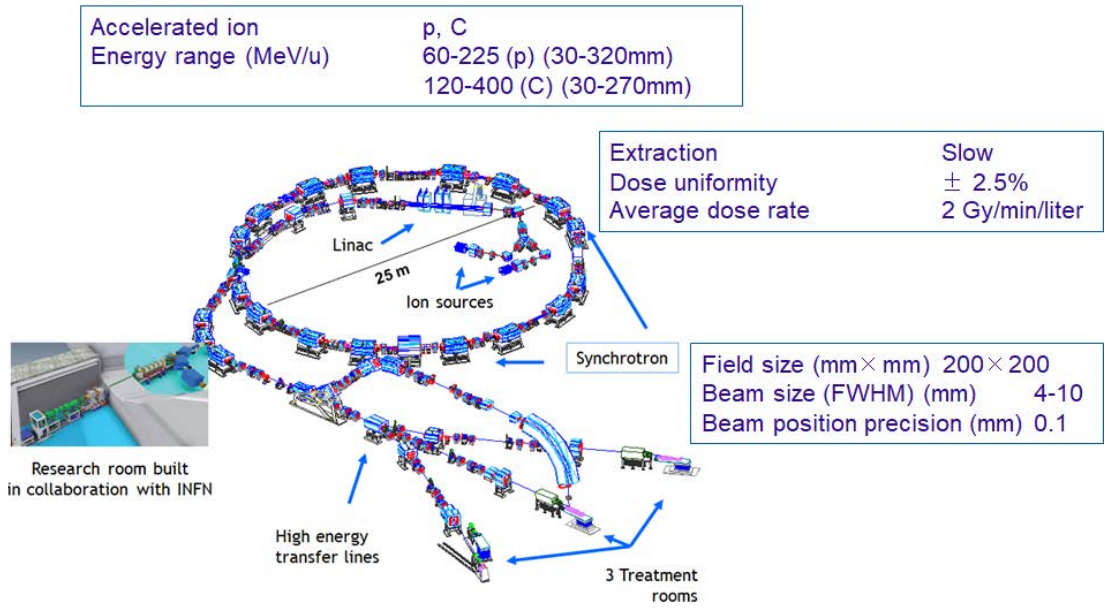


Fig. 4. Model of the PIMMS/TERA synchrotron and tables with main specifications.

directors and presidents from the six founding institutions (including major Milan and Pave hospitals). Erminio Borloni was nominated President of the CNAO Board and held the office from 2001 to 2018. He had the great merit of introducing the managerial culture necessary to realize and start such a Centre.

3. 2003-2010: Construction in Pavia and First Beam

In January 2003, the Italian Government and the Ministry of Health selected Pavia as the definitive location for the CNAO, choosing a site near the Policlinico San Matteo.

By the end of 2003, TERA formally transferred to the CNAO Foundation the complete intellectual property, documented in approximately 3,000 pages of technical specifications and drawings. This vast technical package integrated contributions from CERN, GSI, and INFN. In parallel, 16 full-time TERA employees and 9 part-time consultants transitioned to CNAO, forming the foundational technical core responsible for the realization and the managing of the facility. This team was guided by Sandro Rossi, who had been in service as TERA Technical Director since 1995 and later became CNAO Technical Director. In 2004, Professor Roberto Orecchia was appointed as the Medical Director of the CNAO Foundation.

In 2004, the INFN officially joined the CNAO Foundation as an Institutional Participant, taking on substantial technical responsibilities during the construction phase.

The procurement process involved numerous tendering procedures throughout 2004 and into 2005 for both the high-technology components (including the synchrotron magnets and injection linac) and the civil engineering works. Construction of the underground bunker began in Summer 2005. The initial construction phase included three treatment rooms dedicated to protons and carbon ions, accommodating particle beams up to 400 MeV/u, with future provisions for other treatment rooms.

The project achieved a significant milestone on October 15, 2010, when the first proton beam was successfully extracted from the CNAO synchrotron.

4. Present days: Clinical activities and Upgrades

After completing construction in 2010, the facility has been routinely delivering patient treatments with both protons and carbon ions since 2011. CNAO is rec-

ognized as one of the only eight multi-ion centres in the world. As a functional public healthcare structure, the facility currently operates three treatment rooms for routine usage (each with a horizontal beam, and one also having a vertical beamline).

By the middle of 2025, CNAO had treated more than 5700 patients with carbon ions accounting for 50% of treatments, and protons for the remainder. The Italian National Health System provides reimbursements for hadron therapy treatments across ten specific clinical indications. The range of tumours treated at CNAO includes those located near critical structures or characterized by radio-resistance. Specifically, key indications involve chordomas and chondrosarcomas of the skull base and spine. CNAO also focuses on complex Head and Neck (H&N) tumours, such as adenoid cystic carcinoma (ACC), sinonasal cancers (SNC), and mucosal melanomas (MM), benefiting from the higher relative biological effectiveness (RBE) of carbon ions. Other major disease sites treated are various soft-tissue and bone sarcomas, including those of the axial skeleton and pelvis, as well as tumours of the orbit, particularly ocular melanoma. Furthermore, since three years, CNAO has treated about 300 paediatric patients affected by solid tumours. Specific treatment sites also include high-risk prostate cancer, local recurrent rectal cancers, certain gynaecological malignancies and recurrent tumours (re-treatment) in previously irradiated areas. Central nervous system tumours like meningiomas and low-grade gliomas are also typically considered for particle therapy, due to the need for critical organ sparing. The overall undistinguished local control is close to 85% and a range between 10% and 30% of increase in survival rate, with good quality of life, is observed with respect to conventional treatments with X rays.

Beyond clinical activity, CNAO maintains a fourth room entirely dedicated to research, allocating over 600 hours in 2024 to beam time and labs for the research community.

A significant expansion, named CNAO 2.0, is currently underway, based on a preliminary design by the TERA Foundation, which received financing and approval in 2018. The realization phase of the additional buildings is completed and new technologies are coming up. Fig. 5 shows a recent photo of CNAO.

This expansion introduces three major technological upgrades: a new Proton Gantry System with a dedicated accelerator. This system, supplied by Hitachi Ltd., ensures independent productivity, offers a crucial back-up



Fig. 5. Photo of CNAO from the nearby San Matteo hospital.

solution, and expands therapeutic options by allowing the beam to move around the patient, thereby reducing patient positioning times; a Boron Neutron Capture Therapy (BNCT) facility intended for dedicated clinical and research activities, aiming to treatment of diffuse tumours, leveraging the recent innovation of accelerator-based neutron sources; a third ion source, named AISHa (Advanced Ion Source for Hadrontherapy), completed and installed in the Fall of 2023 in collaboration with INFN. This source enables the production of novel ion species ranging from Helium to Iron, which are valuable for bio-spatial research and multi-ion personalized treatments. CNAO aims to utilize these new capabilities (multi-ion treatments, gantry use for complex cases, and BNCT research) to face the “second border”, particularly targeting metastatic cancers through new generation hadron accelerators and targeted medicines.

The CNAO Foundation is currently chaired by President Gianluca Vago, who is reckoned as ensuring a successful future in the clinical and research fields. Ugo Amaldi has still a central role in the Foundation, having been appointed as Honorary President and permanent member of the Board. The CNAO workforce, led by Sandro Rossi as Director General, counts 170 individuals, with 90 women and an average age of 40. Notably, 77% of the staff hold a University degree, and 40% of them hold a PhD or a Master’s degree. This diverse team represents 19 different professional roles, ranging from doctors and physicists to radiobiologists, technicians, bioengineers, and administrative staff.

5. Amaldi’s legacy, not just CNAO: other programmes of the TERA Foundation

In May 2001 at Orta San Giulio (Novara, Italy) the 10th anniversary of the TERA Foundation was held. This was the occasion to take “the picture of the situation” and analyse the evolution of the activities launched during the first decade. It was also a turning point for TERA, since between the end of 2000 and the beginning of 2001 the new CNAO Foundation was established, with the intention of constructing and running the CNAO project.

The scientific initiatives of TERA were mainly divided into three programmes:

- *TERANET* Programme: informatics dedicated to health purposes;
- *COMPACT ACCELERATORS* Programme: novel medical accelerators at contained costs;
- *CENTRES OF EXCELLENCE* Programme: design and realisation in Italy and in Europe of complete and advanced systems for the treatment of tumours through radiations.

During the nineties, TERA created the associations *TERA Friends*, the *European Scientific Institute* and the unipersonal society *Physalus srl*. These three organisms were chaired by Ugo Amaldi to guarantee the communion of purposes with TERA. Synthetically, they can be said to represent the TERA answers to the necessity of (1) having its roots on the territory, (2) informing and training and (3) supporting the burden of transferring

the results of its research to society. It is not possible here to outline all the activities and results obtained by such a galaxy build by the TERA Foundation and its President Ugo Amaldi, but here we will only focus on the most advanced technological programme apart from CNAO: the LIBO project.

6. The compact accelerators programme: the linac booster (LIBO)

In 1993, Amaldi and his work group initiated the study of a novel *proton* linear accelerator based on the *same high radio frequency* ($f = 3$ GHz) as the one used by thousands of *electron* accelerators running in hospitals all over the world [4].

The design of a 3 GHz proton linac was tackled in the general framework of a study of novel, so-called ‘compact accelerators’. These studies were concentrated on four different types of accelerators: a compact conventional synchrotron, a high-field synchrotron, a superconducting cyclotron and a 3 GHz linac. The results are described in the ‘Green Book’ [5]. The comparison among the different modalities pointed out the advantages of the linac solution:

- the output energy is variable, and even faster than in a synchrotron;

- the time structure is very well suited for the application of the spot-scanning technique;
- the transverse beam emittances are about ten times smaller than the typical emittances of cyclotrons and synchrotrons, requiring much smaller gaps in the dipole magnets of the gantry, thus considerably reducing their weight and cost.

It was clear from the beginning that the linac could also be used downstream of a cyclotron, to boost the low energy of the beam delivered by a standard commercial cyclotron (about 30 MeV) to 200 MeV or more, as needed for deep protontherapy. To such a linac, the name LIBO, which stands for LINac BOoster, was given. This was the focus of the work over the years from 1997 to 2003.

In 2001, the prototype module of LIBO was built and successfully tested at CERN and LNS labs of INFN in Catania (Italy), where it accelerated 62 MeV protons to an energy of 73 MeV, in agreement with the results of the simulations. The working principle of LIBO has thus been fully demonstrated (Fig. 6). At present, the LIBO prototype is lodged at the CERN exhibition.

7. The last born: the TERA-CARE Foundation

In August 2023, Ugo Amaldi promoted the creation of a Swiss Foundation in Geneva named TERA-CARE

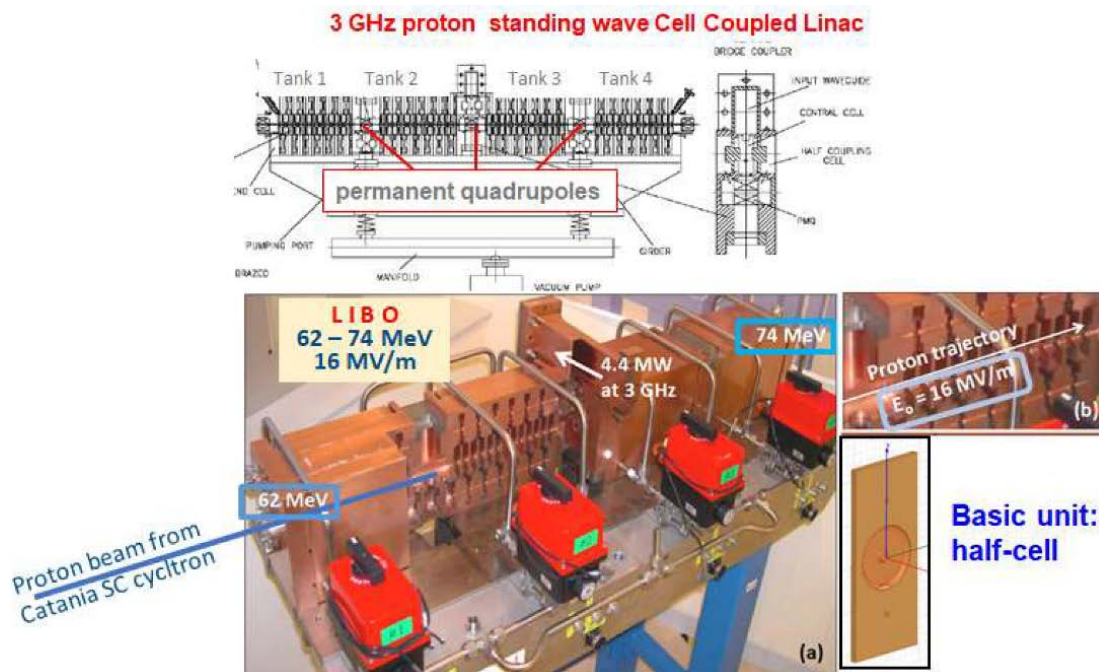


Fig. 6. Prototype of LIBO built at CERN, within a collaboration among TERA, CERN, INFN (Milan and Naples sections).

(www.tera-care.ch), with funds donated by a Sponsor who, 20 years before, had financed TERA for the design of CNAO. The Sponsor, having participated in the Symposium held on September 2022 at CERN for the 30th Anniversary of TERA, was inspired by the many achievements and the more than 200 young physicists and engineers, mostly trained at CERN, where the TERA scientific team has its offices and laboratories.

In collaboration with international players active in radiation medicine, TERA-CARE aims at improving the technologies to diagnose and fight cancer and at saving lives via three programmes (Fig. 7):

A. the Hadron Therapy Programme, focused on the design and the construction, in Middle- and High-Income Countries, of novel synchrotrons for treating tumours with hadrons: in particular, with beams of helium ions;

B. the Nuclear Medicine Programme, that aims to produce novel medical radioisotopes, in particular Astatine-211, for ‘theragnostics’, which combines diagnostic imaging and therapy through the injection of labelled molecules;

C. the Low-Income Countries Radiotherapy Programme, that trains radiation oncologists and technicians of Low-Income Countries and participates in the design and realisation of a robust X-ray radiation system adapted to challenging environments.

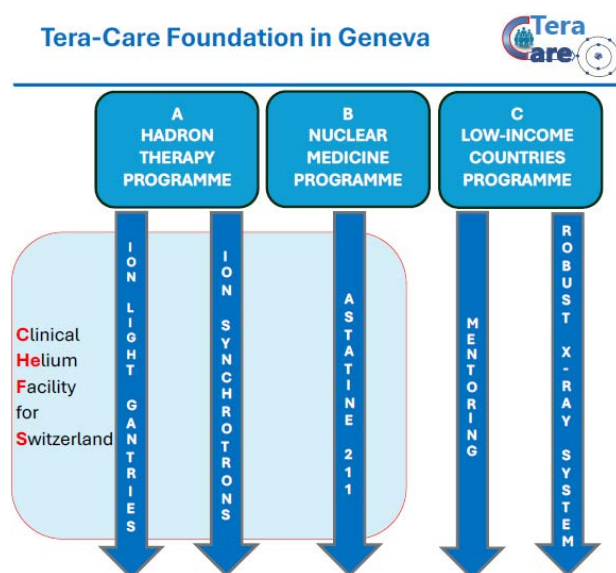


Fig. 7. The programmes of Tera-Care.

Conclusions

We have just entered the fourth decade of TERA and CNAO: a successful story originated by Ugo Amaldi's idea in 1991.

CNAO's vessel has reached its first dock. Cultivating the *myth* within themselves, like the Argonauts, the girls and boys of TERA and CNAO have continued to sail, facing sometimes stormy seas, continuously repairing the planking, never interrupting the navigation. The dream came true and CNAO is now a human, scientific, clinical, and organizational machine that operates day after day always looking ahead. Ahead is CNAO2.0, dreamed, imagined, designed and almost ready to face the second border, new research horizons, and the therapy, hitherto unthinkable and unspeakable, of metastatic cancers to be countered by a new generation of hadron accelerators and targeted medicines.

Other programmes of the TERA Foundation have experienced remarkable successes throughout the last four decades and, thanks to the innovative programs of the TERA-CARE Foundation, the future is once again bright and full of promising possibilities.

The phenomenology of growth and development acted by TERA and CNAO rely on distinctive values inspired by Ugo Amaldi and his activity through the years (Fig. 8).



Resilience - “Ci vuole pazienza”



Prominence of scientific approach to problems



Precision and attention to details



Collaboration spirit



Take care of persons



Ethical attitude

Fig. 8. Values inspired by Ugo Amaldi and now common practice in TERA and CNAO activities.

Confident in these values, within the same physical and organizational space, specialists from very distant disciplines coexist, interacting and cooperating with one another. Although they run the constant risk of reliving

the sense of bewilderment that struck the builders of the Tower of Babel narrated in the Scriptures, they have managed to elaborate together and co-construct a conversation in which the measurements detected by the

“technology’s” control systems, therapeutic protocols, administrative compliance, research projects, and many more characteristics of the numerous professions present, intersect and mutually feed one another.

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