# Overview of the Tumour Therapy Facilities with C-Ions in Europe

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This document presents a short overview of the existing Tumour Hadron Therapy Facilities for protons and C-ions in Europe and their relation to the proposed SEEIIST facility in South East Europe. It starts with the role of GSI and CERN in the major R&D work for the facilities and then lists the central features of HIT in Heidelberg, CNAO in Pavia and MedAustron in Vienna. MIT in Marburg, the Siemens derivative of HIT and as such unrepeatable since the retreat of Siemens from this market, is not treated here. The features discussed include the investment costs, the operational costs, the time development of the patient treatments and the role of research besides patient treatments. References to the details are given below. The SEEIIST facility, presented for the first time to the Public at the Forum in Trieste in January 2018, is described in Ref. [1,2] and is integrated here where applicable.

1. The central role of GSI and CERN for the R&D of the facilities

The technical developments of the facilities, in particular of the medical accelerators, have their roots in major European Physics Laboratories: for HIT the national GSI Helmholtz Center for Heavy Ion Research in Darmstadt, for CNAO and MedAustron the European Laboratory CERN in Geneva.

At GSI, considerations for a medical synchrotron date back to the late 1970s under the influence of the Bevalac work at LBL. The formation of a biophysics group at GSI by G. Kraft with pioneering results on the DNA response to ions as well as on technical aspects of patient treatments greatly helped the further discussions during the 1980s. As a unique feature, active medical interest entered almost in parallel, represented since 1987 by M. Wannenmacher, Medical Director of the Radio-Oncological Clinic of the University of Heidelberg. The coherent approach of physics and medicine was the decisive prerequisite for the Directorate decision at GSI in 1993 to treat the first patients in Europe with C-Ions from the existing synchrotron SIS18 in a collaboration of GSI, of the Radio-Oncological Clinic in Heidelberg and of the German Cancer Research Center DKFZ in Heidelberg. The FZR Rossendorf contributed with an on-line PET. About 440 patients were treated during 1997-2008, with most remarkable successes. The formal proposal for the clinic machine HIT in Heidelberg, the central driving force of the local patient treatments, was made in 1998, with the detailed design work completed a few years later. The younger generation responsible for the patient treatments at GSI later formed the core of the technical and medical team of HIT.

An independent initiative for Tumour Hadron Therapy including ions was followed up in parallel by U. Amaldi in Italy since 1991, joined later by M. Regler with interest for such a facility also in Austria. In the early 1990s, legal carriers were founded, and on the Initiative of U. Amaldi the Proton-Ion Medical Machine Study (PIMMS) Group was formed at CERN, following an agreement between the TERA Foundation and the MedAustron group to combine their efforts in the design of a tumour therapy synchrotron. CERN agreed to host this study in the PS division under its leadership. The PIMMS team started its work in 1996 [3]. A strong educational program for young scientists and technicians from the participating countries (about 50 in case of MedAustron) was an essential part of the later planning, and it were dominantly those people who were responsible for the later construction of the facilities CNAO located in Pavia and MedAustron in Wiener Neustadt.

Great credit has to be given to both GSI and CERN for these prime examples of large-scale technology transfer, much beyond of what could normally be expected from Laboratories primarily devoted to fundamental research.

2. Investment costs

HIT was constructed under the formal roof of a GmbH structure, but attached to the Heidelberg University Clinic. The investment costs are 119 MEuro, funded to 50% each by the Clinic and the

German BMBF [4,5]. However, since HIT contains a gantry (the first for heavy ions worldwide), only 90-95 MEuro should be compared to the CNAO costs which do not yet include a gantry, and to the MedAustron costs corrected for its proton gantry. The HIT costs contain the building, all hardware components produced by various industrial companies with the Arge SIT as General Contractor, 4 rooms (3 treatment rooms by Siemens Medical Solutions, 1 room for research), and 70 man-years of technical personnel of GSI Darmstadt (5 MEuro) which built up the overall system in Heidelberg. The rather low investment costs also reflect the full integration into the workflow of a large RadioOncological Clinic which provides all required infrastructure for the patients like reception, full medical diagnostics, anaesthesia, administration etc. Patient treatment started in 2009. HIT is led by J. Debus as the Scientific-Medical and T. Haberer as the Scientific-Technical Director. Both of them carried a leadership role already for the patient treatments at GSI. J. Debus is also the Director of the full Radio-Oncological Clinic as the successor of M. Wannenmacher.

The CNAO facility (6,7) has its origin in the TERA Foundation, founded 1992 by U. Amaldi, which started R&D work for a medical machine with a strong manpower effort. Following the PIMMS design study at CERN, the CNAO Foundation was founded in 2001 to construct the later center in Pavia based on that design, taking over much of the personnel of TERA. Founding members of CNAO were, among other organizations, a number of clinics in Italy, assuring in this way the core of the later medical use of the facility. The center was then built under the CNAO roof on the basis of subcontracts with a large number of industrial companies. The investment costs of CNAO are 135 MEuro [7], including the building (45 MEuro) and the construction costs (with presently 3 treatment rooms). The additional costs compared to HIT reflect at least partially the character of a stand-alone facility not connected to a special clinic, where specific investments are required for the missing infrastructure. Patient treatment started in 2011. The Scientific Director of CNAO is R. Orecchia, the General Director is S. Rossi who was already a member of the PIMMS team.

The situation is somewhat similar for Med-Austron [9-10], also based on the PIMMS design. The construction of the facility was also not done by CERN, but under the roof of the EBG MedAustron GmbH (founded in 2007) by a large team of young scientists and engineers educated and trained at CERN as outlined above, and also here on the basis of subcontracts with a large number of industrial companies. The investment costs including building and construction are officially cited as 200 MEuro [9]. There are 3 treatment rooms (one with a proton gantry) and 1 for research. Subtraction of the costs of the proton gantry leads to about 185-190 MEuro, which is the number to be compared to the 135 MEuro of CNAO and the 90-95 MEuro of HIT (w/o the ion gantry). Additional investments due to the stand-alone character of the facility have also been necessary here, as in case of CNAO. Patient treatment (only with protons) started in 2016. Administrative GF is A. Zens, Medical GF is E.B. Hug, leader of the accelerator is P. Urschuetz.

The costs of CNAO and the detailed initial experience in Pavia have been the basis for the extrapolated base number of 165 MEuro for the SEEIIST facility [1], where the construction costs have been accurately re-evaluated piece by piece in contacts with industry. This includes 2 rooms for patient treatments and 1 for research. An ultimate upgrade to 4 rooms for patient treatments including a proton and an ion gantry and 2 rooms for research would increase the total investments costs to about 200 MEuro [1]. No incremental costs are contained for any additional infrastructure in case that an attachment to a local special oncological/radiological clinic is not possible.

## 3. Operational costs

HIT in Germany quotes [5] 5.5 MEuro/year for its personnel of 70 experts (Medical Doctors, Medical-Technical Assistents and Nurses, Physicists, Engineers and Technicians), 1.1 MEuro/year for electricity (3 MW for 7d/24h), and a less sharply defined amount for maintenance, depreciation etc., adding up to the order of 10-11 MEuro/year. This as well as the additional clinic costs required for the infrastructure are covered by the patient income via the illness insurance system (prepared already during the GSI time). The operation of HIT is thus fully sustainable. The operational costs of CNAO are 17 MEuro/year [8], higher than for HIT because of its higher personnel of ultimately 140 FTE (for the projected 850 Patients/year) and of the additional infrastructure costs connected with the autarky of the facility without attachment to a clinic. For MedAustron no official value is presently available.

The operational costs of the initial 3-room SEEIIST facility have been estimated [1] to be 10-11 MEuro/year, based on a total personnel of about 80 with a significantly reduced salary level compared to Western European countries [1]. This covers the medical, technical and local research personnel, power and maintenance, but not the further infrastructure required without attachment to an existing clinic.

## 4. Patient potential and actual treatments

Hadron therapy with ions heavier than protons, like C-ions, has been the driving force behind the facilities in Europe under discussion here. Proton therapy is an essential by-product, in particular for the treatment of children, but it is not as unique in the sense that dedicated proton accelerators exist since long and are much cheaper. The number of potential patients for C-ion therapy related to the population is judged to be about 200 per 10 million people in 'first level priority' [1,8]. For Germany, this implies about 1600/year, for Italy 1200/year, for Austria 200/year, and for the 10 countries expected to participate in the SEEIIST Project including Greece 800/year, without Greece 600/year. With proton therapy and research in parallel, the beam time needs mostly exceed the potential of a single machine.

HIT, the first facility in Europe which started in 2009 has reached about 700 patients/year by 2015/16 [5] (about 5000 in 8 years altogether). CNAO which started in 2011 has reached about 500/year by 2017 [7] (about 2000 in 6 years altogether), and MedAustron which started in 2017 about 140 up to 5/2018 [10]. For HIT, the mixture of C-ions and protons is about 1/2 each, for CNAO 2/3 vs. 1/3, while MedAustron has chosen to stage the commissioning and has so far only used protons, with C-ions expected to become available in 2019.

The number of yearly patients foreseen for the 50% beam time of the SEEIIST therapy project is ultimately expected (with 4 rooms) to also be about 500/year [1].

## 5. Coexistence of patient treatments and research

Research is common throughout. HIT routinely has a 7d/24h operation mode, where the treatment of patients uses close to 50% of the beam time during the daytime except for Sundays. The other 50% is a mixture of research (about 25%, biophysics et al.), medical physics and machine aspects [4,5]. CNAO has presently a research fraction up to 15%, but that will increase with a new dedicated beam line in 2019 [6-8]. MedAustron has so far only accelerated protons, but a dedicated beam line with room for research exists as well as the required personnel, assuring a similar level of research as elsewhere for the time of full operation including C-ions.

The SEEIIST facility will place particular emphasis on a full 50% research fraction. Decisive open issues in connection with the understanding of the 'Relative Biological Efficiency' (RBE) of other ions between protons and carbon and even above need to be clarified in order to optimize the choice of the ions and the detailed conditions for patient treatment. This requires a systematic *multi-ion* research programme on the basis of animal experiments, much more so *in vivo* than done so far, and also with large animals. Great interest exists for that also in the global biomedical research community as expressed by the interest in the (former) BioLEIR Project at CERN. This unusually strong emphasis on research will make the SEEIIST facility somewhat unique worldwide.

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