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A Facility for Tumour Therapy and Biomedical Research in South-Eastern Europe

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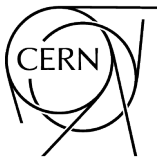

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Abstract

In 2016 the South East European International Institute for Sustainable Technologies (SEEIIST) was proposed by Herwig Schopper and brought to the political level by Sanja Damjanović, Minister of Science of Montenegro. In this framework two design studies have been completed by two groups of European experts: a "4th Generation Synchrotron Light Source for Science and Technology" (SRL) and a "Facility for Tumour Hadron Therapy and Biomedical Research" (HTR). A preliminary report was presented and discussed at the Workshop on "New International Research Facilities for South East Europe" held in January 2017 at ICTP (Trieste). In March 2018 the Steering Committee came unanimously to the conclusion that the first facility to be built should be the HTR. This report contains the HTR study, which was completed in July 2018; the Executive Summary has been written for the readers who are not interested in the details.

Keywords South-Eastern European countries; hadron therapy; particle therapy; proton therapy; carbon ions; ion radiobiology; medical synchrotron; radioresistant tumours.

Editor: Ugo Amaldi

Contents

Executive summary

In 2016, at a Workshop of the World Academy of Art and Science held in Dubrovnik, Professor Herwig Schopper proposed the creation in South-Eastern Europe of an International Institute devoted to sustainable technologies. The objectives of SEEIIST (South East European International Institute for Sustainable Technologies) were, and are, both to create new opportunities for cutting-edge research and technology for the welfare of the region, and to help in the building of mutual trust among scientists and engineers—and also among administrators and politicians—as has been successfully demonstrated by the cases of CERN and SESAME.

Dr Sanja Damjanović, Minister of Science of Montenegro, brought the Initiative to the political level by contacting the relevant Ministers of the South-Eastern Europe (SEE) countries and convincing them to participate in launching it. Given the positive reactions, in Spring 2017 I was asked to organize and chair an Editorial Committee aiming at the preparation of the conceptual design report of a 'Facility for Tumour Hadron Therapy and Biomedical Research' (HTR). Dr Dieter Einfeld was put in charge of the same task in connection with a "4th Generation Synchrotron Light Source for Science and Technology" (SRL).

While the Editorial Committees were working on the conceptual designs of the two facilities, a meeting of the Ministers of Science or their representative took place at CERN on 25 October 2017. The goal was to sign a Declaration of Intent for future collaboration. Albania, Bosnia and Herzegovina, Bulgaria, Kosovo[*], the FYR Macedonia, Montenegro, Serbia, and Slovenia were represented; Croatia agreed 'ad referendum', while Greece participated as an observer. The final declaration stated that the Parties have a common vision and that the Institute shall operate with the mission of 'Science for Peace'.

Following the meeting at CERN, an Intergovernmental Steering Committee was created, and Sanja Damjanović was elected as the chairperson. In this framework on January 25–26, 2018, a Forum on "New International Research Facilities for South East Europe" was organized at ICTP (Trieste), where a first document prepared by the two Editorial Committees and entitled "Basic Concepts for the South East European International Institute for Sustainable Technologies" was distributed, presented, and discussed. The Forum was well attended and the discussions were lively and productive.

In the following two months the Steering Committee met twice—in Sofia (January 29, 2018) and in Tirana (March 30, 2018)—and came unanimously to the conclusion that the first Facility to be built in the Region should be the HTR.

Meanwhile, the two Editorial Committees have continued producing more detailed documents. This Report describes the conceptual design of the Hadron Therapy and Research Facility. I hope that this will be useful, as a starting point, for the experts who will be put in charge, for the next two to three years, of writing the Technical Design Report that will cover all technical, scientific, financial, and legal aspects of the Initiative.

It has been wisely decided by the Steering Committee that the site of the Facility will be chosen at a later stage of the project. Here I want to emphasize that other important decisions will have to be taken at the same time because two collaborative Networks will have to be organized and their hubs are better placed elsewhere so as to involve in the Initiative more Institutions, belonging to different countries, hence enhancing and enlarging the collaboration in the region.

The Networks are essential for the success of the Initiative. Indeed, The Clinical Network will allow the radiation oncologists and related experts of the Region to work together with the oncologists of the Facility and of European and non-European hospitals in developing new protocols and participating in multicentre prospective comparative clinical trials. The Scientific Network of

[*] In this document the designation to Kosovo is without prejudice to positions on status and is in line with UNSC 1244/1999 and the ICJ opinion on the Kosovo Declaration.

Universities, Research Centres, and Hospitals will connect all the groups either currently carrying out or planning experiments in the experimental halls of the Facility.

* * *

In Western Europe about 50% of all tumour patients, corresponding every year to about 2500 patients per million inhabitants, are irradiated with curative intent with ionizing radiation such as X-ray beams produced by medical linear accelerators marketed worldwide by several international companies.

X-ray beams, which are made of a few MeV photons, are produced when electrons, accelerated to about 10 million electronvolts (10 MeV) by a linear accelerator, bombard a heavy metal target. X-rays have the property to traverse the body, thus, many cross-firing X-ray beams are necessary to deposit much larger radiation 'doses' in the tumour target than in the surrounding healthy tissues to preferentially kill the cancerous cells and simultaneously minimize the damage to the surrounding tissues.

In the last twenty years a novel radiation therapy has been introduced: 'hadron therapy' (also called 'charged particle therapy', 'particle therapy', or 'ion beam therapy'). It uses, instead of X-rays, beams of either protons or carbon ions moving at between 30% and 60% of the speed of light. The reason is that a beam of electrically charged ions produces a 'Bragg peak' of high dose just before stopping in the tissues at its target depth. Downstream (upstream) of the Bragg peak, no (or little) dose is deposited so that protons and carbon ions can deliver higher doses to the tumour, sparing much better than X-rays the normal tissues located in front and behind it.

The sensitive target of radiation therapy is the DNA of the traversed cells. The distance between two successive ionizations, i.e., between the events in which an atom or a molecule loses one electron, determine the biological and clinical effects. The radiation is 'sparsely' ('densely') ionizing if this distance is larger (smaller) than the 2–nanometre diameter of the DNA molecule.

Protons have practically the same biological and clinical effects as X-rays because they are both sparsely ionizing radiations. However, since the dose of protons is much more concentrated in the tumour, for the same probability of cure they cause fewer secondary effects in the nearby 'organs at risk' that cannot sustain significant doses because of unacceptable consequences for the patient's quality of life. In particular, it is generally accepted that children should be treated with protons instead of X-rays.

Carbon ions—which are carbon atoms deprived of their six electrons—are a different type of radiation because, in a traversed double helix, a carbon ion produces twenty times more ionization than a proton reaching the same depth in the patient's body. When entering the tissues, carbon ions behave as sparsely ionizing radiations, i.e., as X-rays and protons, but, by slowing down, in the last 3−4 centimetres of their path in the patient's body, they become 'densely ionizing' and produce multiple clustered DNA damages, which cannot be repaired by the usual mechanisms that protect all cells. Thus, the carbon dose is not only more concentrated in the tumour but is also much more effective than X-rays and protons in controlling 'radioresistant' tumours, which are 3–5% of all solid tumours.

X-rays are produced by electron linear accelerators, also called 'linacs', that are 1-metre long copper tubes having a diameter of about 10 centimetres. If proton and carbon ions could be so easily accelerated, X-rays would have a minor part in radiation therapy. However, a therapy accelerator for proton and ion therapy is much larger, and more complex and also costlier than a linac for X-rays.

The configurations of all of the running proton and carbon ion synchrotrons are very similar to the one shown in Fig. S1.

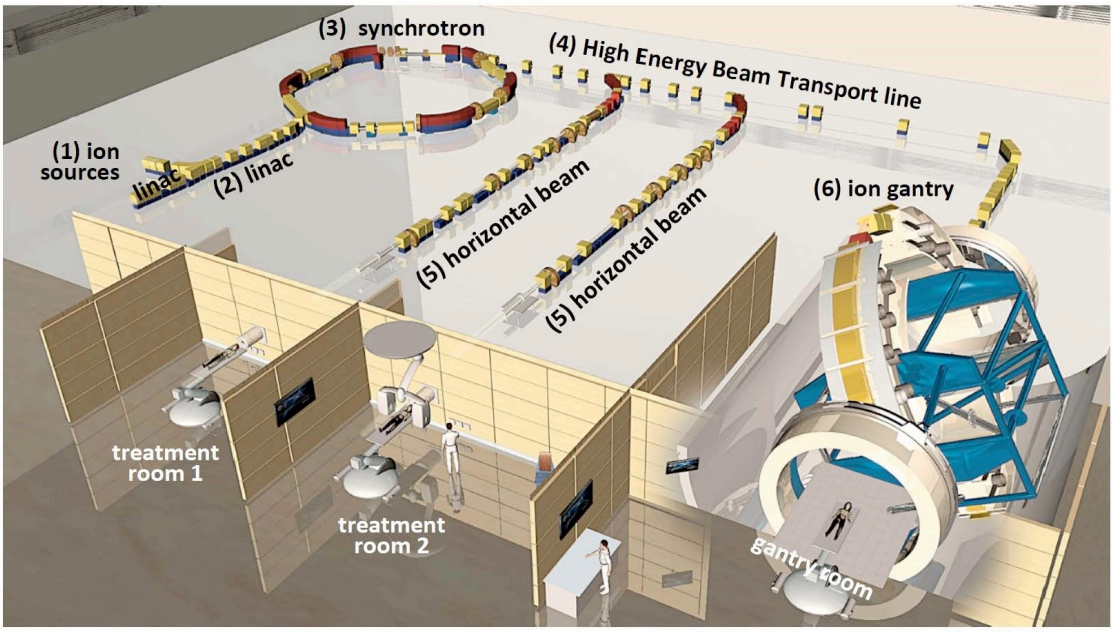

Fig. S1: Layout of Heidelberg Ion Therapy (HIT) Centre in Germany

The schematic drawing of the SEE Facility of Fig. S2 is based on the synchrotron designed at CERN in the 1990s by a CERN-TERA-MedAustron collaboration. Two centres derived from this design are at present treating patients in Pavia (CNAO) and in Wiener Neustadt (MedAustron). This design has been used to estimate the construction and running costs of the Facility.

After an initial start-up period, the proposed Facility will:

A. treat with carbon ions and protons, for about 50% of the daytime and in 2 (and, at a later stage, in 4) treatment rooms, 250 (and later 500) patients/year**,** to cover a large fraction of the yearly number of South-Eastern European patients having tumours of the highest priority for carbon and proton irradiation;

B. do research work, for the remaining fraction of the daytime, plus nights and weekends, on:

   1. in vitro radiobiology experiments**,** to better understand the fundamental mechanisms of radiosensitivity and radioresistance;

   2. animal studies for in vivo determination of the efficacy of carbon and other ions in the treatment of human radioresistant and radiosensitive tumours, and normal tissue effects;

   3. medical physics measurements and development of novel radiation detectors and optimized treatment planning systems.

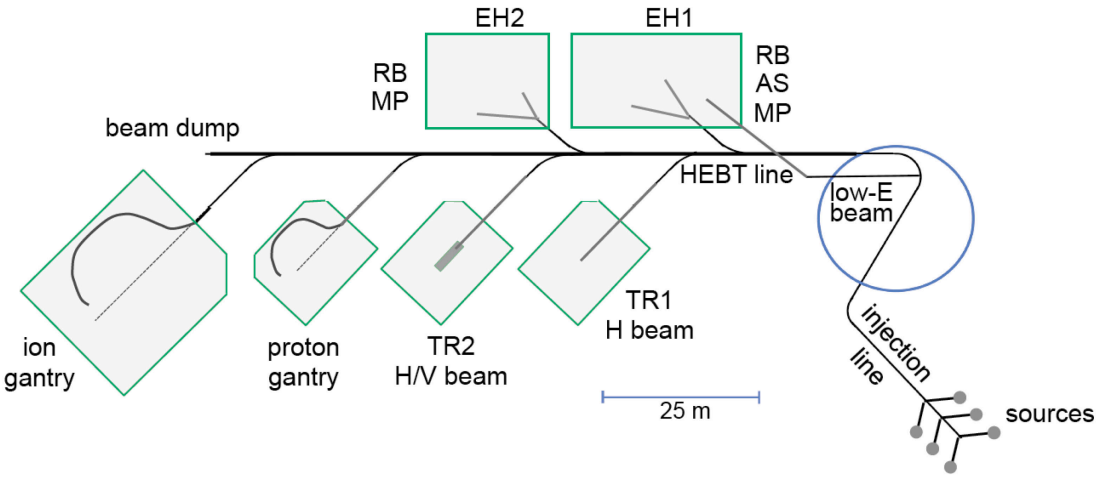

Fig. S2: As discussed in the text, the Facility, which features four treatment rooms and two experimental areas, will be realized in three stages. The total length is about 150 metres.

With the above programmes the Facility will be unique in the world because of the ample time devoted to pre-clinical, radiobiological, and medical physics research. In fact, most of the other facilities concentrate on patient treatment and the time left for the research programmes is insufficient.

As far as **programme A** is concerned, tumours eligible for hadron therapy account for about 10% of all radiotherapy patients, 1% of which are in the very first level of priority. This corresponds to about 280 tumours per year (80 for protons and 200 for carbon ions) for a population of ten million people, so that the Facility of Fig. S2, irradiating about 500 patients per year, will offer a state of the art treatment for often hopeless tumours to about two thirds of the regional population. Recruiting them will be one of the main challenges of this initiative.

For protons the main targets will be solid tumours in children. Carbon ion beams will be used for the highest priority, mostly radioresistant, tumours (adenoid cystic carcinomas of salivary glands, adenocarcinomas of the head, neck, and thorax, mucinous melanomas of the head and neck, chordomas and chondrosarcomas, non-small cell lung carcinomas, hepatocarcinomas of large size, and pelvic relapses of adenocarcinomas). For proton therapy the aim is a significant reduction of toxicity and, for carbon ion therapy, the aim is a gain in cure rate and survival, for mainly radioresistant tumours, from about 50%, achieved with X-rays, to more than 75%.

The time plan foresees at least 1 year for the organization of the Construction Team and the discussion with the potential vendors of the different components. This will be followed by 4 years for the construction and 1 year for the commissioning. It is supposed that the construction site will be a ‘green field’ and that its cost will not be charged to the project.

For **programme B2** an animal facility will be built for the permanent housing of small rodents. Larger animals will be treated in collaboration with an external veterinary department, which can be located in a different country of the Region.

The construction of the treatment rooms and the experimental halls will be staged so that a lower initial investment will, from the beginning, allow significant clinical and research activities. According to a possible scenario, initially the research programmes will be carried out in the first experimental hall (EH1 of Fig. S2) devoted to radiobiology (RB), animal studies (AS), and medical physics (MP), while beams of many different ion species will be available in two treatment rooms (TR1 and TR2) where two horizontal beams and a vertical beam will be available (Fig. S2).

The investment needed for this first stage has been estimated to be 120 M€ that, added to the approximately 45 M€ for buildings (at Western European costs), gives a total of about 165 M€.

The second stage, in which a proton gantry will be installed, will require about 20 M€. With a further 35 M€, the Facility will be completed with an ion gantry and a second experimental hall (EH2).

It has been estimated that for the running of the facility 37 experts will be needed. At the same time 46 people will take care of the clinical, radiobiological, and physics programmes. Moreover, many hundreds of visiting scientists, coming from inside and outside of the Region, will participate in the various scientific programmes.

The running cost will be about 11 M€/year, which will be reduced to 6 M€/year when taking into account the 5 M€/year coming, after a few years of treating patients, from the incomes due to the ~500 patients irradiated every year.

* * *

Training of the young generation is an essential and integral part of the Initiative. The realization of the project will take several years, which gives sufficient time to train not only the future team that will help to build and later operate the installations but also to form a user community.

As anticipated, to reach the clinical and scientific goals, two Networks will be set-up from the beginning of the project and continuously extended: the Clinical Network and the Scientific Network, which will be located in different Institutions.

After an initial period, the two Networks described will be used to recruit the teachers who will train the new experts, coming mainly from SEE, in numbers that exceed the needs of the Facility, so that other hospitals and institutions will eventually employ them, thus raising both the scientific level and the quality of the work done in the Region.

With the building of this Facility there will be many opportunities for technology transfer to the SEE countries. First, the procurement of the different components for the machine and beam lines (magnets, vacuum system, girders, beam lines, power supplies, control system, etc.) can be preferentially assigned to local industries. Second, the Initiative will give rise to spin-offs not directly linked to the facilities but providing an initial spark for new activities in the Region and will promote the development of regional broadband-digital networks.

Ugo Amaldi

Geneva, 30th July 2018

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1 Motivations, goals, and programmes

1.1 Motivations and goals of the South-East Europe Centre for Hadron Therapy and Biomedical Research

Hadron radiation therapy (HT), with beams of protons and carbon ions, is in rapid development so that worldwide, about 70 centres are treating patients and another 70 are under construction (Appendix A).

Protons have biological effects that are not very different to those of X-rays, the standard modality with which more than 5 million people are treated every year worldwide. Protons, however, deliver their energy almost exclusively to the tumour target, thus sparing the surrounding healthy tissues and reducing the negative secondary effects, as well as the long-term induction of new tumours.

Carbon ions are a different type of radiation, because they produce different and more severe damage than X-rays and protons at the end of their range in the patient's body. This increased efficacy allows for control of the so-called 'radioresistant tumours', which are about 5% of all solid tumours and are poorly controlled by either X-rays or protons.

In spite of the fact that, by the end of 2017, more than 160,000 patients had been treated with protons and 25,000 with carbon ions, clinical research is still needed, in particular in the quantitative determination of the augmented efficacy for tumours and normal tissues and in the choice of the ion species which produce the best clinical outcome for all of the very different types of radioresistant tumours. It has to be added that

(i) carbon ions may not be an optimal choice for all types of tumours and that the exploration of other possibilities (e.g., lighter ions such as helium or heavier ions such as oxygen ions) requires long-range planning and years of study;

(ii) any clinical research programme has to be based on solid data and models, in particular on the accurate simulation of the radiation field (*in silico*) and on experiments performed with cell cultures (in vitro) and with animals (in vivo).

Very few two-arm studies have been completed to compare the clinical results of X-rays, hadron beams, and other modalities (Appendix B). This is due both to the way in which these modalities have been historically implemented and, more recently, to the lack of facilities devoted to experimental and clinical research.

On the basis of these arguments, the Facility described in this report is intended to be a centre open to medical doctors and scientists coming from European and non-European countries. Its staff members will work in close collaboration with external experts:

(i) to treat, when completed, during 50% of the daytime, with carbon and other ions, about 500 patients/year, who will participate in multicentre clinical studies;

(ii) to work, for the remaining 50% of the daytime, plus nights and weekends, on:
- radiobiology experiments;
- animal studies;
- medical physics measurements and model development;

(iii) to contribute to the establishment and implementation of new techniques and methods in the clinical and scientific fields listed under (i) and (ii).

For the animal studies programme, an animal facility for rodents will be available in the Centre. Larger animals will be irradiated in collaboration with a veterinary department.

Medical imaging instrumentation, i.e., CT, PET, and MRI, will be needed in the facility, which will not have patient beds. However, the Centre will be built close to a hospital that will provide beds, in the rare cases in which they are needed, and of course general medical care. If possible, the

availability of a radiation oncology department with linacs for X-ray therapy and the corresponding medical imaging tools, in that nearby hospital would be very useful. This will reduce the variety of diagnostic instruments to be installed at the Facility. (The radiation departments of the SEE countries are listed in Appendix C.)

For radiobiology experiments the Centre will feature a low-energy beam (7−8 MeV/u) and a high-energy beam (up to 430 MeV/u). This low-energy beam can be also employed for material science and, in particular, for ion beam analysis (IBA), material modifications, and radiation hardness studies (Appendix D).

1.2 Physical and radiobiological bases of X-ray and proton therapy

In Europe, about 50% of all tumour patients (i.e., about 2,500 patients per 1 million inhabitants every year) are irradiated with X-ray beams produced when electrons, accelerated by a linear accelerator to about 10 million electronvolts (10 MeV), bombard a heavy metal target (Fig. 1). The X-ray beam is shaped as a transverse section of the tumour target by a 'multileaf collimator' made of computer-controlled movable metal fingers.

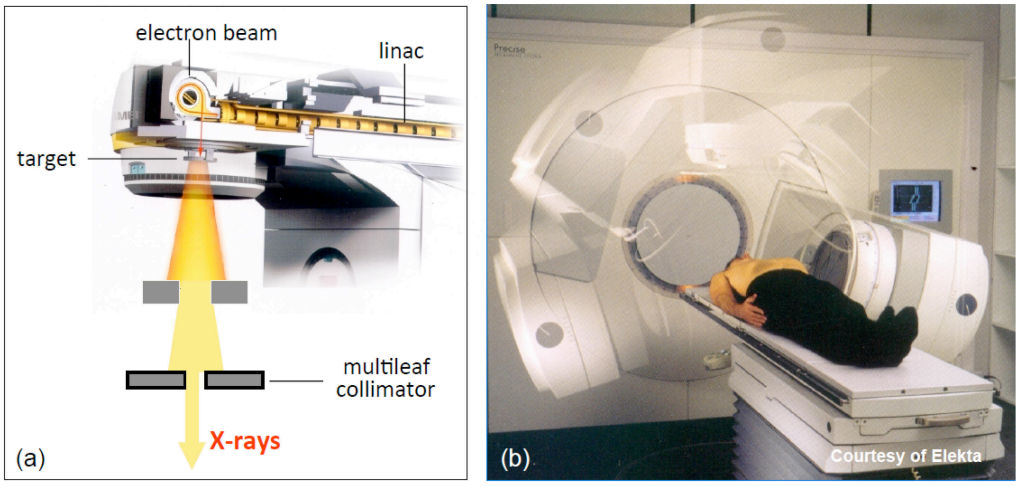

Fig. 1: The linac (a), the magnets that deflect the electron beam by 270°, the target, and the collimators are mounted on a 'gantry' that rotates around the patient (b).

Radiation oncologists use worldwide about 30,000 electron linear accelerators (linacs), more than half of all the running accelerators with energies larger than 1 MeV. Today radiation therapy (RT) with X-rays is by far the most cost-effective cancer treatment.

The aim of a radiation treatment is to deposit in the tumour target a large enough energy per unit of mass—a quantity specified by the 'radiation dose' that is the energy absorbed by a unit of mass; the radiation dose is measured in 'grays': 1 Gy = 1 joule/kg. This energy is not transferred directly by the 1−10 MeV photons, constituting the X-ray beam, but indirectly by the electrons that are put in motion by the photons and, before stopping with a tortuous path that is about ten millimetres long, lose energy in two ways:

(i) by promoting the electrons of the traversed atoms and molecules to a state of higher energy in a phenomenon called molecular 'excitation';

(ii) by 'ejecting' atomic electrons, most of which, in turn, excite atoms and eject other electrons in a phenomenon called molecular 'ionization'.

Immediately afterwards, the excited molecules go back to their normal state so that the main result of a radiation beam crossing a piece of matter is the deposition of energy in the form of ionization of its atoms and molecules. The local radiation 'dose' can be conveniently thought of as the energy left by the beam, in the form of ionization, in a unit mass of tissue. About 70% of this energy is

absorbed by water molecules and produces reactive oxygen species (ROS), i.e., simple molecules containing oxygen, which are chemically very aggressive and are usually called 'free radicals' or 'oxidants'. By diffusing in the cell these radicals can arrive on the DNA molecule and break it either on one strand (*single strand break*, SSB) or on both strands (*double strand break*, DSB) producing, sometimes, clustered damage. Because of its importance the DNA molecule is protected by an elaborate repair system that restores, with high fidelity, the SSBs and most of the DSBs. The unrepaired breaks can cause the death of the cell; on average, only one out of about 50 DSBs is lethal to the cell. These indirect effects of the X-ray beam on DNA are, obviously, chemical phenomena.

ROS are activated in oxygenated tissues and deactivated in hypoxic ones. For this reason hypoxic tumour cells tend to be 'radioresistant', i.e., to require larger X-ray doses to be severely damaged. Hypoxic cells are found at the centre of some large tumours but there are also tumours that are radioresistant without being hypoxic. Globally, about 5% of the tumours treated by radiation are very radioresistant. They are the major problem of conventional radiotherapy since the cure rate is low because, often, the X-ray dose cannot be increased, as necessary for their control, without irradiating nearby critical organs that cannot be irradiated without compromising the patient's quality of life.

About 70% of the deposited energy produces indirect effects mediated by free radicals. For the other approximately 30%, direct effects are at work: one of the electrons, put in motion by the X-ray photons, crosses the double helix and, by ejecting electrons, produces directly either an SSB or, more rarely, a DSB. This is a physical phenomenon. In reality the situation is more complex, but the distinction between indirect and direct effects remains broadly valid and can be usefully employed in comparing the effects on tissues of X-rays and hadron beam.

1.2.1 Dose distributions and treatment schemes in X-ray therapy

As shown by the blue curve of Fig. 2, the depth−dose distribution of a conventional X-ray beam, after reaching a maximum at a few cm depth, is characterized by an almost exponential attenuation and absorption of the dose, and consequently delivers the maximum dose near the beam entrance, but continues to deposit significant amounts of energy at distances beyond the cancer target until it exits.

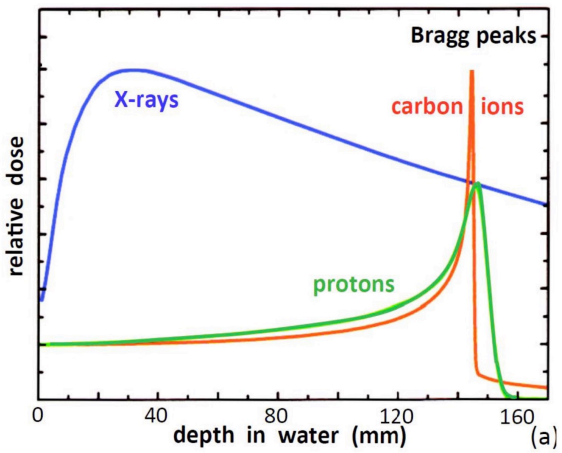

Fig. 2: Comparison of depth dose profiles of high-energy photon (X-rays, in blue), protons (green), and carbon ions (red) beams. The abscissa is the depth in water or in a soft tissue.

The X-ray dose determines the clinical effects of the treatment, which are well documented for both normal and cancerous tissues thanks to more than 100 years of study[‡].

Since, as shown in Fig. 2, after 10−20 millimetres the relative dose decreases with the depth, the clinical effects also decrease. To concentrate the dose and produce the larger curative effects in the

[‡] Recently, new effects of the autoimmune system and characteristics of the cancer stem cells have been discovered and it is not excluded that these new understandings will bring benefits to future patients.

tumour target, the X-ray dose is given from many directions by rotating the electron linac around the patient and modulating the shape and intensity of each beam using computer-controlled 'multileaf' collimators (Fig. 1).

The example given in Fig. 3, which refers to a large skull base tumour, shows that—to minimize the dose given to normal tissues—X-rays are crossed-fired from 9 directions; still, the colour scale indicates that surrounding normal tissues receive doses that are as large as 50% of the dose given to the tumour.

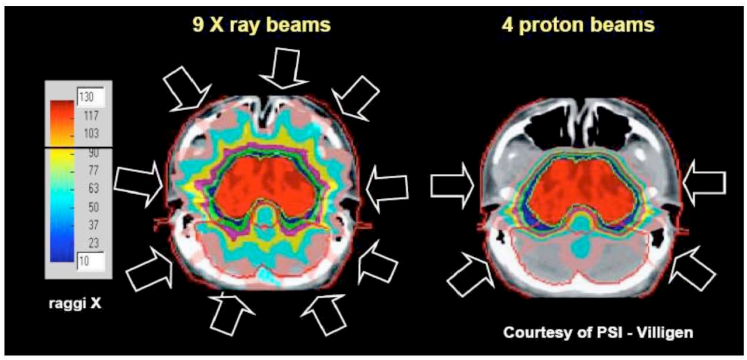

Fig. 3: With 9 non-coplanar X-ray beams the dose to this large skull base tumour is very uniform and the brain stem (in green) can be spared, but large doses are given to the whole brain (left-hand figure). In the case of 4 proton (or carbon ions) beams the situation is much more favourable (right-hand figure).

With these techniques of cross-firing, called *intensity modulated radiation therapy* (IMRT), a very 'conformal' X-ray treatment can be given at the expense of a greater integral dose, which is unavoidably deposited in the normal tissues surrounding the target because, as shown in Fig. 2, the X-ray dose is distributed all along the path in the patient's body.

In a typical treatment with X-rays a total dose of 60−70 Grays is deposited in a tumour target in 25−35 daily fractions over 5−7 weeks in order to give allow for unavoidably irradiated healthy cells and tissues to repair the radiation damage. Interestingly, this fractionation principle makes possible some re-oxygenation of hypoxic, and therefore radioresistant, tumour cells and the transition of tumour cells from radio-resistant cell cycle stages to more sensitive stages.

1.2.2 Physical bases of hadron therapy

The heart of an electron linear accelerator—called also the 'linac'—is small and light: a very special 1-metre long copper tube that has a diameter of about 10 cm (Fig. 1). The linac is mounted on a gantry that rotates around the couch where the patient is lying, so that the beam of X-rays produced when the accelerated electrons hit a heavy metal target can be directed towards the solid tumour from any direction. Conversely, hadron accelerators are larger, weightier, and costlier than X-ray electron linacs because a proton (carbon ion) is 2,000 (24,000) times heavier than an electron and has to be accelerated to about 200 MeV (5,000 MeV), instead of 10 MeV, to treat a 30-centimetre deep tumour. Instead of linear accelerators, circular ones are needed, called 'cyclotrons' and 'synchrotrons', in which bunches of particles are bent by powerful magnets on a circular path and at every turn get a small energy increase.

Proton therapy cyclotrons are nowadays superconducting with a diameter of about 1.5 metres, but also synchrotrons are used. For treating 300 mm deep solid tumours, a typical 230 MeV therapy synchrotron for protons has a diameter of 6−8 metres and the magnets, which bend the beam on a circular path, weigh tens of tons. Since a carbon ion is made up of 6 protons and 6 neutrons and has to be accelerated to 5,000 MeV, to treat the same tumour target, the diameter of an ion synchrotron has to be about 3 times larger, i.e., 18−25 metres. In these synchrotrons the groups of particles are injected at energies of about 100 MeV by a special 'injector' linac and circulate for one second corresponding to about one million turns.

The layout of the Heidelberg Ion Therapy Centre (HIT) is shown in Fig. 4.

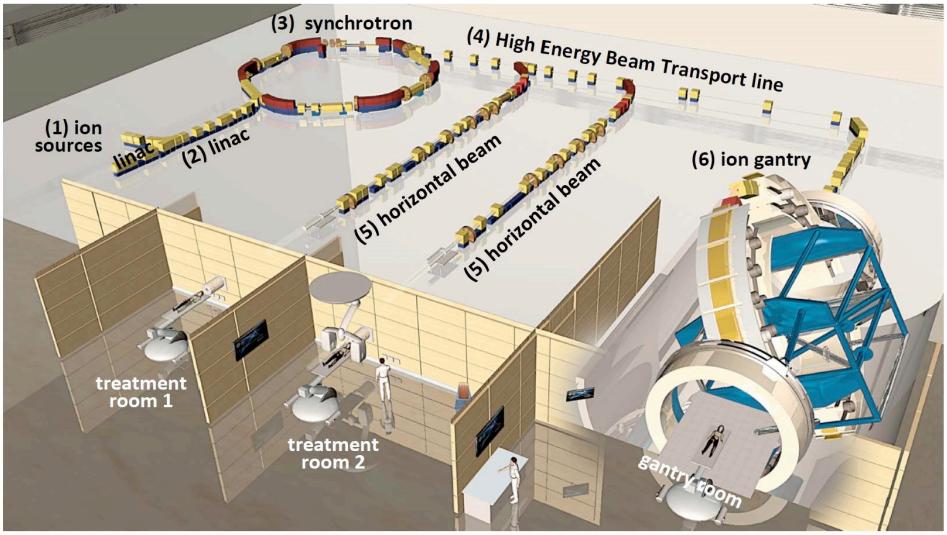

Fig. 4: Layout of HIT Centre in Heidelberg. By the end of 2017, HIT, which was the first European carbon ion and proton centre, had treated 4,700 patients with carbon ions.

The configurations of all the running ion synchrotrons are very similar. Typically, they feature:

(i) two (or more) ion sources;

(ii) an injector linac;

(iii) a synchrotron;

(iv) a high energy beam transport line, made of magnets that focus the beam;

(v) one or more horizontal beamlines, equipped with instruments that 'paint' the tumour and produce dose distributions similar to the one of Fig. 3 (right-hand side);

(vi) sometimes a carbon ion gantry that rotates around the patient couch.

As shown in Fig. 3 (right-hand side), with a proton or a carbon ion beam a uniform dose can be deposited in a tumour target, of any shape and with any location in the body, sparing normal healthy tissues much better than X-rays. This is due to the fact that, in matter, hadrons move practically in straight lines so that the Bragg peaks of Fig. 2 give origin to the 'spot' shown in Fig. 5.

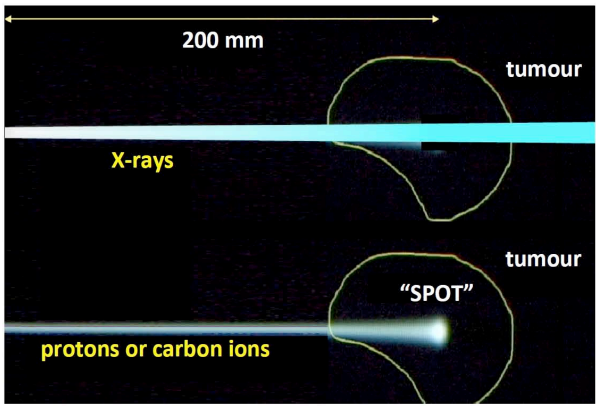

Fig. 5: In water (and also in soft tissues) the Bragg peak gives origin to a three-dimensional spot that is at a depth of 200 mm when the energies of the protons and carbon ions are 170 MeV and 4,000 MeV, respectively.

The transverse dimensions of a 200−300 mm deep spot are about 10 mm in the case of protons and about 4 mm in the case of carbon ions. Another difference, not shown in Fig. 5, is that in the

carbon case downstream of the spots there is a small 'tail' (shown in red in Fig. 2) due to the fragmentation of a fraction of the carbon ions into smaller nuclei, ending their course a little further than the Bragg peak.

Due to the Bragg spot it is possible to concentrate the proton and carbon ion doses on the tumour target, sparing much better than with X-rays the normal tissues located in front of and behind it. Since the doses are more 'conformal' to the target, radiation oncologists can increase the hadron dose to the tumour while depositing the same dose as with X-rays in the healthy tissues, thus increasing the cure rate with the same secondary effects. Alternatively, by giving with hadrons the same dose to the tumour as with X-rays—and thus having the same cure rate—one can reduce secondary effects in normal tissues such as, for instance, the long-term probability of secondary tumours.

1.2.3 Radiobiological bases of hadron therapy

Along most of their paths in the patient's body, energetic protons break the DNA indirectly, through the mediation of the same reactive oxygen species produced by X-rays. As for X-rays, only about 30% of the deposited dose causes direct damage to the double helix. Because of this, for the same dose to the tumour target, the biological and clinical effects of protons are similar to those of X-rays.

However, there is an on-going debate in how far a substantially increased effectiveness that is also observed in vitro at lower proton energies is of clinical relevance, as it might show up at the distal edge of the treatment field. Systematic experimental in vivo data are lacking here, which could help to clarify both the proton effects in the last millimetres of their range in biological tissues and the clinical consequences of the nuclear interactions of protons and other ions[§].

Since protons behave biologically and clinically similarly to X-rays, most clinical protocols for proton therapy take advantage of the knowledge accumulated over more than a hundred years of conventional radiotherapy and adapt it with only slight modifications for proton therapy. In particular, the dose is typically subdivided into 20−30 fractions over 4−6 weeks.

Given the more conformal dose distributions of protons with respect to X-rays, the indications for proton therapy are clear: they are to be preferred when a high enough dose cannot be deposited in the tumour target because a nearby critical organ limits the maximum allowable dose. As said above, the higher conformity can be used either to increase the dose to the tumour or to decrease the damage to normal tissues. Proton therapy is well suited to the cases where the tumour is radiosensitive (about 95% of the cases) and the fast fall-off of the dose allows for the depositing of a larger dose in the target for the same dose as X-rays in the surrounding normal tissues.

It has to be remarked that a larger dose is beneficial because dose−response curves are typically very steep, and even a modest 10% increase of the dose deposited in a tumour gives typically an increased probability of local control of the tumour itself by about 20%. This implies, theoretically, that passing from 60 Gy to 66 Gy, the control probability increases from 50% to 70%, a non-negligible gain.

Treatment protocols are well defined and, by the end of 2017, more than 160,000 patients had been treated with proton beams. Today, many radiation oncologists think protons should be used for about 10% of the adult cases, those for which the tumour is close to organs at risk, which are organs that, if heavily irradiated, would cause a serious deterioration of the patient quality of life.

About 1% of these adult cases (corresponding to about 25 patients in a population of 1 million people) are high priority cases. Moreover, it is now generally agreed that solid tumours in children (6−7 children patients in a population of 1 million people) should be treated with curative intent with protons and not with X-rays.

[§] At present, the differences between protons and X-rays are a topical argument. See, for instance, Ref. [1]

1.3 Radiobiological bases of carbon ion therapy

Although protons and carbon ions show similar depth−dose profiles, the lateral scattering is reduced for heavier ions and the Bragg spot of a carbon pencil beam is transversally and longitudinally smaller. On the other hand, as said above, carbon and other ions show a small dose contribution beyond the Bragg peak, which is the result of the fragmentation of the ions, leading to lighter nuclei with a longer range in matter.

1.3.1 Relative Biological Effectiveness and Linear Energy Transfer of carbon ions

Because of the smaller spots in both the lateral and the longitudinal directions, carbon beams exhibit dose gradients about three times steeper than protons. But the main advantage of carbon ions as compared to protons is the significantly increased *relative biological effectiveness* (RBE) in the last centimetres of the carbon range in tissues. The meaning of RBE can be understood from Fig. 6.

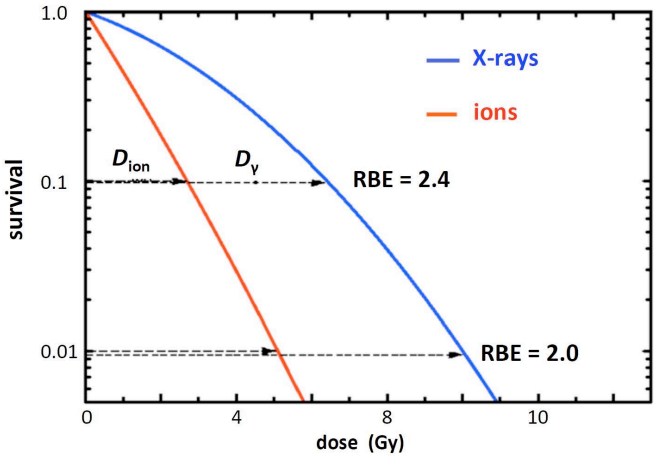

Fig. 6: Example of calculation of two RBE values from the survival curves of cultivated cells irradiated with a photon beam and a carbon ion beam having linear energy transfer (LET) = 200 eV/nm = 200 keV/µm.

RBE is defined as the ratio of the reference dose D_X (usually due to X-rays produced by 200−250 keV electrons) to the dose D_{ion} necessary to produce the *same* biological effect, e.g., survival of 10% of the cells, with ion irradiation:

$$\mathrm{RBE} = [D_X / D_{ion}]_{\text{same effect}} \quad . \qquad (1)$$

The figure shows that at the 10% survival level, RBE = 2.4 while at the 1% survival level RBE= 2.0, demonstrating in a simple example that the RBE value depends on the considered biological or clinical effect.

The quantity ‘dose’ is a macroscopic parameter that does not describe the microscopic structure of the energy deposition events. It is the spatial distribution of the ionization along and around the particle trajectory—called the ‘track structure’—that determines the biological effects.

One important scale for the understanding of the specific high-LET effects is the diameter of the DNA molecule, about 2 nanometres, as the DNA represents the main target of the radiation attack inside the cell. However, also other scales e.g., on the level of chromatin organization (so called ‘giant loops’ with a size of the order of 1 µm) and the cell nuclear size (about 10 µm) are known to be of particular relevance.

The relevance of the nm scale is illustrated in Fig. 7, indicating the decrease of the average distance between two successive ionizations (indicated by the letter ‘*d*’ in Fig. 7a) when a carbon ion penetrates in the patient body, losing energy until it stops.

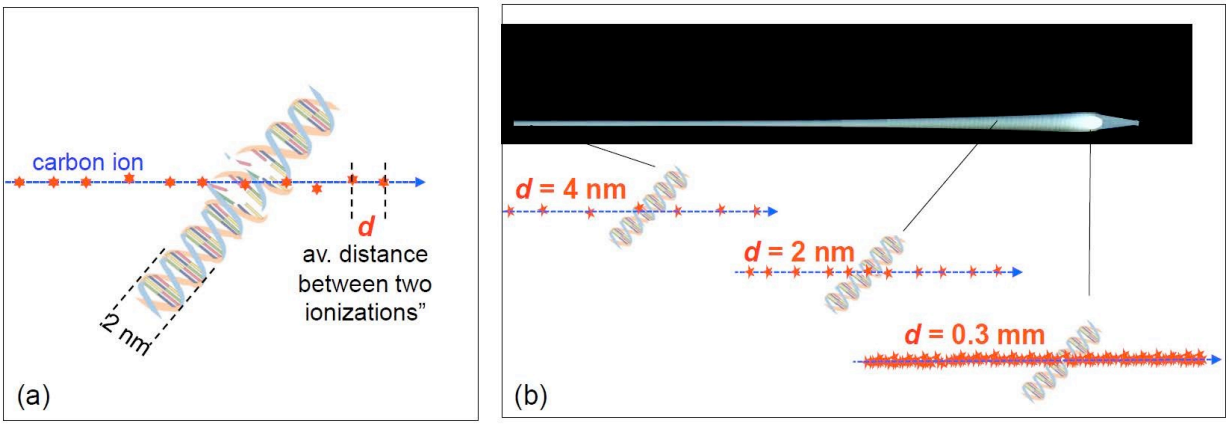

Fig. 7: (a) A parameter defining the biological effect is the average distance *d* between two ionizations. (b) The value of *d* decreases when the energy of the ion decreases during the slowing down process and is equal to 2 nm for a residual range R = 40 mm.

This can be understood quantitatively by introducing the energy lost by the charged hadron in a unit track length called 'linear energy transfer' (LET), which can be expressed as a function of the effective charge Z_{eff} , the mass number A (which is the total number of protons and neutrons), and the speed $\beta = v/c$ of the projectile:

$$\mathrm{LET} = const \;\; Z^2_{eff} \,/\, (A\,\beta^2) \,. \qquad (2)$$

Equation (2) highlights the most relevant dependencies of the so-called Bethe−Bloch formula, which determines the shape of the Bragg peak:

(i) the rise of the energy deposition with depth as a consequence of the decreasing energy, and thus speed β; and

(ii) the drop, after reaching the maximum, as a consequence of the particle charge Z, which captures atomic electrons and becomes $Z_{eff} < Z$.

Point 1 can be made more explicit by writing Eq. (2) as an approximate function of the 'residual range' *R* in water (or in soft tissues):

$$\mathrm{LET} \approx 5.0\, Z^{1.13}\, A^{\,0.435} \,/\, R^{0.435} \quad (R \text{ in mm of water; LET in eV/nm = keV/μm}) \,. \qquad (3)$$

The formula expresses the fact that the Bragg peak—shown in Fig. 2 and exploited in all hadron therapy treatments—has the form $1/R^{0.435}$, i.e., it is roughly proportional to the inverse of the square root of R[**]. Moreover, at equal distances *R* from the stopping point, a carbon ion (Z = 6, A = 12) is characterized by a LET, and hence by an ionization density that is 22 times larger than that of a proton (Z = 1, A = 1)[††]. This large ratio is at the root of the different radiobiological and clinical effects of carbon ions and protons.

1.3.2 Carbon ions are radiobiologically different from X-rays and protons

For a given ion species, the LET value is the main determinant of the ion RBE. A typical behaviour is shown in Fig. 8 for a cell type often used in radiobiological studies.

[**] In the last millimetres the divergence of Eq. (2) when *R* goes to zero is washed out by the fact that particles penetrating the matter have different ranges when the paths are measured from the entrance point. This phenomenon is due to the statistical fluctuations of the events in which high-energy electrons are put in motion ('straggling').

[††] For helium the ratio is 4.

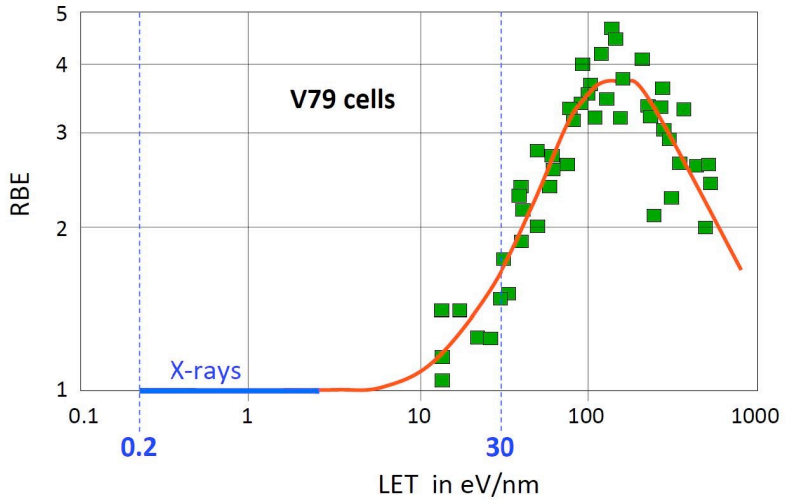

Fig. 8: RBE versus LET for a 10% cell survival. By definition X-rays have RBE = 1.

The figure shows that when, during the slowing down process, the LET becomes larger than about 30 eV/nm (equivalently, larger than 30 keV/µm or 300 MeV/cm), the RBE increases sharply, attaining values larger than 3 for LET ≈ 200 eV/nm, and then drops towards higher LET values as a consequence of saturation effects that are equivalent to a waste of energy (so called 'overkill').

The value 30 eV/nm can be qualitatively understood because a particle with LET = 30 eV/nm leaves, on average, in the 2 nm double helix 60 eV, and about 30 eV are needed to produce one ionization. For LET larger than about 30 eV/nm, the ionizations are so close along the ion track (with d less than 1 nm, on average) that one speaks of 'densely ionizing' radiation. This corresponds to a few ionizations per nm, which is of the order of magnitude to induce, by independent ionization, either a DSB or a more severe clustered damage.

Due to the frequent ejection (due to statistical fluctuations) of more than one electron at high LET when crossing the DNA molecule, severe DNA lesions called 'clustered not-reparable damage' are produced. This damage hinders the cell cycle, stops the tumour growth, and also may induce the cell internal programme for its own destruction (apoptosis), yielding a fast tumour regression.

Most cells and tissues show this general behaviour, but for different cells and endpoints, the exact shape and position of the LET dependence of RBE may vary, as discussed in Section 1.4.

In general, one can state

$$1 \leq \text{RBE} \leq 5 \qquad \text{for carbon ions ,} \tag{4}$$

Although the range of RBE values is very similar for protons, they exhibit the increased effectiveness only at the very distal end of their penetration depth, whereas for carbon ions the elevated RBE is spread over a larger depth; these differential characteristics are discussed in more detail in Section 1.4.

Summing up, the electrons put in motion by X-rays are sparsely ionizing because the average distance between ionizations is much larger than 1 nm. Also protons are sparsely ionizing, apart from the last millimetre before stopping. Through the chemical mediation of ROS, about 70% of the dose, deposited by these two sparsely ionizing radiations, produces spatially well-separated indirect effects, in particular, the double strand breaks that induce the cell death when they are not repaired.

In clinical practice the similarity of the phenomena induced by protons and X-rays beams translates into the generalized use of a single value for the RBE:

$$\text{RBE} = 1.1 \qquad \text{for protons.} \tag{5}$$

The radiobiological and clinical effects of carbon ions are different because they are densely ionizing. In particular, in the last couple of centimetres of their range, where the tumour tissues are located, *d* is smaller than 1 nm and they behave as a different type of radiation with respect to X-rays and protons: about 70% of the deposited dose produces directly closely spaced damage that, not being mediated by ROS, is insensitive to the oxygen content of the tissue and produces not-reparable clustered damage to the DNA. Because of this behaviour the tumours, which are radioresistant to both X-rays and protons, i.e., about 5% of all solid tumours, are the elective targets of carbon and other light ions.

Since in X-ray and proton treatments the total dose is deposited in many sessions, to allow the normal cells to repair during the intervening days, and with carbon ions the repair mechanisms are not effective, when using carbon ion beams it is possible to cut the number of sessions from 25−30 to 10−15, thus reducing the stress to the patient and lowering the treatment cost.

1.3.3 RBE-weighted dose

In treating patients with carbon and other light ions, the knowledge of the radiobiological effectiveness, to apply to both tumour and normal tissues, is crucial because the radiation field must be quantified by giving the 'RBE-weighted' dose

$$D_{\mathrm{RBE}} = \mathrm{RBE} \times D \,, \qquad (6)$$

which is reported as Gy RBE) and is obtained by multiplying the physical dose D by the RBE value of that particular tissue.

Although conceptually simple, Eq. (6) needs to be applied with caution in the clinical environment because RBE of a tissue is not just characterized by a single value, but depends on several factors, first of all the LET and the considered effect level. Thus, RBE varies within the irradiated volume, whereas for photon radiation the effectiveness is the same throughout the irradiated volume.

Two typical dose response curves are shown in Fig. 6. The blue one refers to X-rays and features a 'shoulder' that is due to the repair mechanism of the DSBs induced by a sparsely ionizing radiation. Instead, for carbon ions (red curve) at LET values around 200 eV/nm (and thus at their maximum effectiveness) the shape of the dose-response curve is almost linear (in a logarithmic scale) because the clustered damage produced by a densely ionizing radiation is not repaired. These different shapes are at the origin of the fact that the RBE value depends on the chosen survival rate, i.e., of the dose per session.

When applying Eq. (6) the percentage error on the RBE-weighted dose D_{RBE} equals the percentage error on RBE and thus the precise characterization of RBE and its dependencies on the relevant physical and biological factors is of utmost importance. Data for cells cultivated in vitro are available, such as the ones shown in Fig. 6, but cells and tissues in vivo may behave differently and only systematic animal studies and accumulated human treatment data can provide the information needed for planning the irradiation of human patients.

A reduction of uncertainties is highly desirable and thus many well-conceived experiments will be needed to gather enough information and reduce the error on D_{RBE} to less than ±5%. Note that in X-ray treatments the error on the dose D, which is the only relevant quantity, is required to be smaller than ±2.5%.

In a treatment planning software, the increased radiobiological effectiveness is integrated into a model that describes the radiosensitivity of normal and cancerous tissues. The most used of these in Europe is the *local effect model* (LEM) developed at GSI, the research Laboratory close to Darmstadt [2]. This model is based on the complete three-dimensional distribution of the ionization and damage around the track and knowledge about the photon dose−response curve for the endpoint of interest; it allows the descriptions of biological effects in vitro and in vivo.

In summary, carbon ion beams of about 5,000 MeV are indicated for treatment of deep-seated tumours, which are radio resistant both to X-rays and to protons. These types of tumour are thus the elective targets in a carbon ion facility.

In general, the major determinants that need to be considered are:

(i) the enhancement of RBE, particularly pronounced in the Bragg peak, and which varies with the residual range of the particle;

(ii) the decrease of ions' RBE with increasing dose per session (Fig. 6); thus, the subdivision of the total dose in fractions is an important parameter that affects the RBE;

(iii) the higher RBE of ions for cells that manifest a higher repair capacity and thus are resistant to photon radiation as compared to cells showing a higher sensitivity to photon radiation;

(iv) the biological effects of ions less sensitive to oxygen concentration as compared to conventional radiation.

The relevance of these factors has been clearly demonstrated in numerous in vitro and in vivo experimental approaches but many experiments have still to be performed both for cell monolayers in vitro or small animals in vivo.

The Centre described in the present report will greatly contribute to this programme since the existing facilities are not sufficient.

1.4 Therapy with other ions

1.4.1 RBE versus LET for various ion species

The Centre will feature several ion sources and numerous in vitro—in vivo experiments and clinical studies will be performed, in collaboration with other ion Centres, to understand which ions are best suited to treat the many different tumour types.

The biological and clinical phenomena are complex and determined by many parameters, but the main aspects can be illustrated by means of the compilation shown in Fig. 9. This compares RBE (LET) curves, as predicted by the local effect model, for a variety of different ion species from protons to Ne ions. The segments shown as thick lines indicate the range of LET values for which the residual range, computed from Eq. (3), is in the interval from 20 mm (lower end of the thick line) to 1 mm (upper end). The most prominent features of this comparison are the shift of the curves to higher LET values when increasing the atomic number of the ion species.

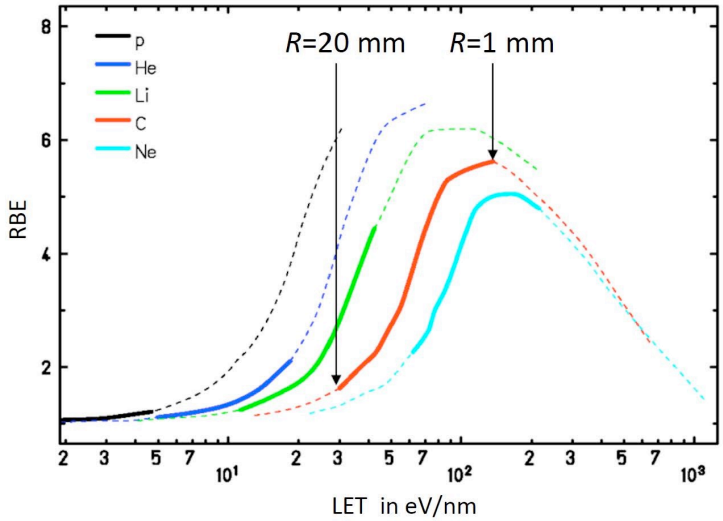

Fig. 9: The local effect model, in agreement with experiments, predicts that the RBE curves peak at larger LETs when the ion charge increases.

Obviously, LET is not a good parameter to characterize the RBE for different particles, as in general the lighter particles show a higher RBE as compared to the heavier particles at a given LET. This can be explained by the dependencies in Eq. (2): lighter particles with smaller charge require a lower velocity, and thus energy, as compared to the heavier particles to have the same LET. At lower energy, however, the lateral spread of the energy deposition within individual particle tracks is smaller, leading to a higher energy density and consequentially also higher biological damage density, finally resulting in the higher RBE.

However, despite the fact that the expected maximal RBE values are very similar for the different ion species, this does not directly translate into similar clinically relevant RBE values. In order to assess those, one needs to consider the range of LET values reflecting similar geometrical conditions with respect to penetration depth and to estimate the variation of RBE across the tumour.

For example, if a tumour of 20 mm diameter is considered, this variation can be characterized by the spread of RBE values between ions with 1 mm remaining range, representative of the distal edge, and with 20 mm remaining range, representative of the proximal edge of the tumour. This spread of RBE values is shown in Fig. 9 by the full line segments. From this it becomes obvious that, in the case of protons, only the lower part of the RBE (LET) curve can be exploited in therapy, whereas in carbon ion therapy the complete rising branch of the curve is exploited.

When going to even heavier ions, such as neon, however, at the distal edge saturation effects dominate, whereas the RBE is already substantially elevated upstream of the proximal edge, i.e., in the normal tissue. This has been, unfortunately, demonstrated in the 1980s at the Bevalac of the Lawrence Radiation Laboratory, where many patients were treated with neon ions with unexpected side effects, since, even for deep-seated tumours, the patients were irradiated with densely ionizing radiation with elevated RBE all along the particle range.

Essentially for this reason, while at the end of the 1980s the preferred ion was oxygen-16, in 1994 at NIRS, Hirohito Tsujii and his collaborators, concerned by the possible effects of oxygen ions on normal tissues, initiated the irradiations with carbon ions. Apart from some 400 patients treated in Berkeley with helium and other small trials, until today carbon ions are the preferred choice, but it is certainly not necessarily optimal for all radioresistant tumours.

1.4.2 Choosing the optimal ion therapy

Many additional factors need to be considered for the choice of the optimal ion species for a given treatment scenario, and realistic treatment planning comparisons are required for the decision about the optimal ion species.

These planning studies should be based e.g., on the comparison of the RBE-weighted dose in the target region as compared to the RBE-weighted dose in the surrounding normal tissue. Here, the essentially different radiobiological characteristic of the tumour and normal tissue are of particular relevance, as in general they are connected with different RBE values.

In addition, since RBE also depends on the dose level, the field configuration (1-field vs. 2-field) and fractionation scheme will play key roles in the assessment of the optimal ion. Finally, within the target, hypoxia can substantially alter the radiosensitivity of the corresponding tumour region and with that also the expected RBE, and in these cases even heavier ions than carbon, such as for example oxygen ion beams, may have additional benefits, as they show a more reduced sensitivity to hypoxia.

It is obvious from this discussion that a large number of well planned and complementary in vitro and in vivo studies have to be performed to clarify and define which ion(s) have the largest control probability for which types of tumour with minimal side effects. Given the ample time dedicated to experimental studies, the SEE Facility has the potential of greatly contributing to this ambitious programme, which will last for decades because the radiobiological results will have to be validated by multicentre phase II and III clinical trials.

1.5 Techniques of hadron therapy

1.5.1 European Centres for carbon ion and proton therapy

The carbon ion and proton 'dual' centre represented in Fig. 4 was designed by GSI and built with the technical support of Siemens Medical. It was the first in Europe and followed the GSI 'Pilot Project' that treated 440 patients with carbon ions in the years across the new millennium. The centres at Marburg and Shanghai, established by Siemens Company, are further direct descendants of the pilot project. By the end of 2017 HIT, has treated 4,700 patients with carbon ions.

Two European proton and carbon ion centres have their roots at CERN, which was involved in their design. They are shown in Figs. 10 and 11.

Fig. 10: Perspective view of the CNAO centre, which features 3 treatment rooms with 4 therapeutic beams (3 horizontal and 1 vertical), and 1 experimental room (not represented).

In fact, in 1996, CERN, the TERA Foundation, and the MedAustron group initiated, under the leadership of Phil Bryant, the *Proton and Ion Medical Machine Study* (PIMMS) with the aim of designing a synchrotron and corresponding beam lines that would be optimized for light ion therapy. The two light ion centres are CNAO in Pavia (first proton patient in 2011) and MedAustron in Wiener Neustadt (first proton patient in 2016).

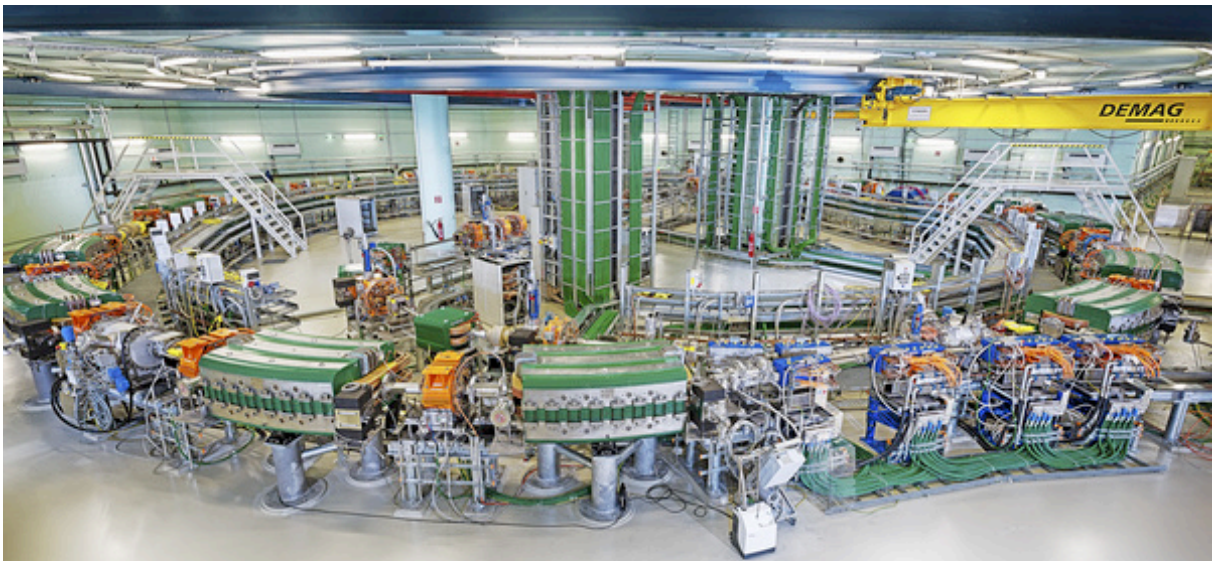

Fig. 11: The MedAustron synchrotron feeds 1 proton treatment room with rotating gantry, 2 light ions treatment rooms with 3 beams (2 horizontal and 1 vertical), and 1 experimental room.

By the end of 2017 CNAO had treated 1,600 patients (75% with carbon ions) and MedAustron had treated about 100 patients (with protons); carbon ion therapy is planned for the middle of 2018.

1.5.2 Active dose delivery

In all hadron therapy centres until 1997 relatively simple 'passive spreading systems' have been used to produce a spread out Bragg peak similar to the one of Fig. 12.

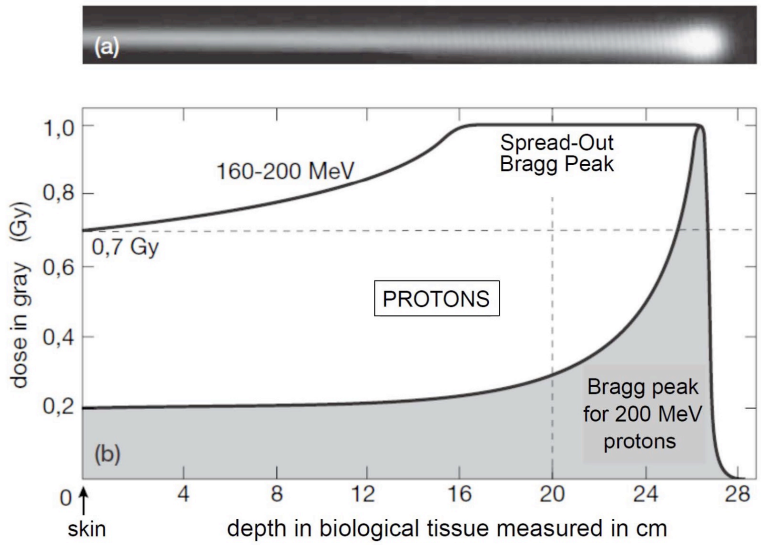

Fig. 12: (a) Penetrating into a biological tissue a narrow mono-energetic proton (carbon ion) beam produces a Bragg spot that has a diameter not smaller than 10 mm (4 mm). (b) Numerous superimposed Bragg peaks at progressively reduced depths give a uniform dose to a tumour of 10 cm length.

Only in 1997 GSI [3] and PSI [4] developed novel 'active spreading systems' where the charged hadrons form a 'pencil beam', having transverse full widths at half maximum in the 4−10 mm range, which is magnetically deflected over the treatment area and modulated in intensity (*intensity modulated particle therapy* = IMPT).

In the GSI 'active spreading' technique used with synchrotrons, which is called 'raster scanning', the target volume is divided into slices of equal ion energy and each slice is divided into small volumes. These 'planned spots' or 'voxels' (i.e., 3-dimensional pixels) are treated separately by moving the Bragg peak in the transverse plane, by means of two orthogonal bending magnets placed a few metres upstream of the patient, and then the beam of constant current is kept fixed for the time needed to deposit the dose determined by the treatment plan. When one slice has been treated, the energy of the beam is reduced for the next slice. In practice, the complete target volume consists of 5,000–15,000 voxels, which are treated in 2−6 minutes.

For mono-energetic ions the Bragg peak is very narrow, so that the energy of the particles has to be changed during the irradiation to cover the tumour depth. In cyclotrons, the beam energy cannot be varied, so that movable energy absorbers and magnetic selection systems have to be used to adapt the range of the particles to the depth of the target to be irradiated. In synchrotrons it is easy to vary the energy of the extracted beam.

In 1994 the first patient was treated with a carbon ion beam at the National Institute of Radiological Sciences (NIRS, Chiba, Japan), which since then has been the pioneering centre for this type of radiotherapy. For about twenty years HIMAC patients have been treated with passive dose spreading techniques, in which the beam energy is changed every synchrotron beam spill. At present, the more effective active spreading techniques are used in almost all the centres. Fig. 13 shows the main elements installed on a beam line (and on a gantry) in order to perform irradiation with such a modality.

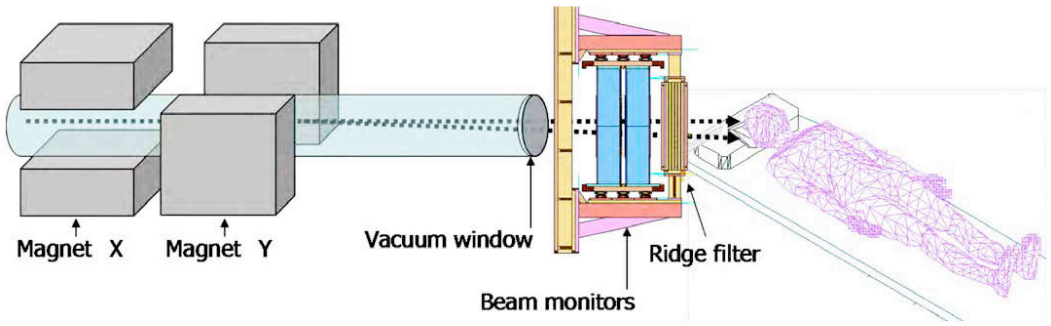

Fig. 13: Localization of the elements of an active delivery system and beam monitors with respect to the patient treatment table.

The delivery system includes: two scanning magnets, the monitoring system, the high-accuracy robotic patient positioning, a six degrees of freedom couch, and the in-room imaging devices for position verification.

At the isocentre the scanning magnets move the beam transversally with a speed that is typically 20 m/s. The beam position is checked in real time with a redundant system of monitor chambers. To apply 4D irradiation strategies this on-line monitoring system is integrated with instruments for the detection of the patient respiratory motion.

1.5.3 Rotating gantries

Systems similar to that of Fig. 13 are also mounted on large mechanical structures that rotate around the patient. The IBA proton gantry of Fig. 14 has a diameter of 3.7 m.

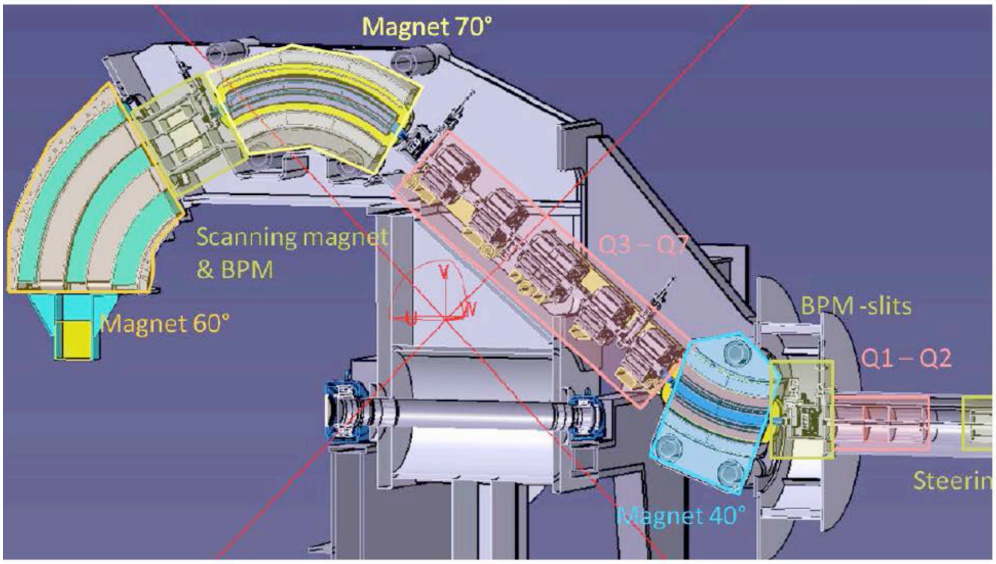

Fig. 14: The 230 MeV IBA 'compact' proton gantry weighs 110 tons.

Since the 'rigidity' of carbon ions having the same range as 230 MeV protons is almost three times larger, the gantries are larger and/or reach a higher magnetic field. The HIT gantry of Fig. 15 weighs about 600 tons and at maximum field consumes about 400 kW. Superconducting magnets allow higher magnetic fields and thus lower weights and much lower power. For the past few years patients have been treated at the CHIBA centre of NIRS with the superconducting gantry of Fig. 15. At present in Japan the advanced superconducting gantry of Fig. 16 is under development. Many laboratories and companies are pursuing the same goal so that, when the SEE Facility ion gantry will have to be chosen there will be various valuable alternatives.

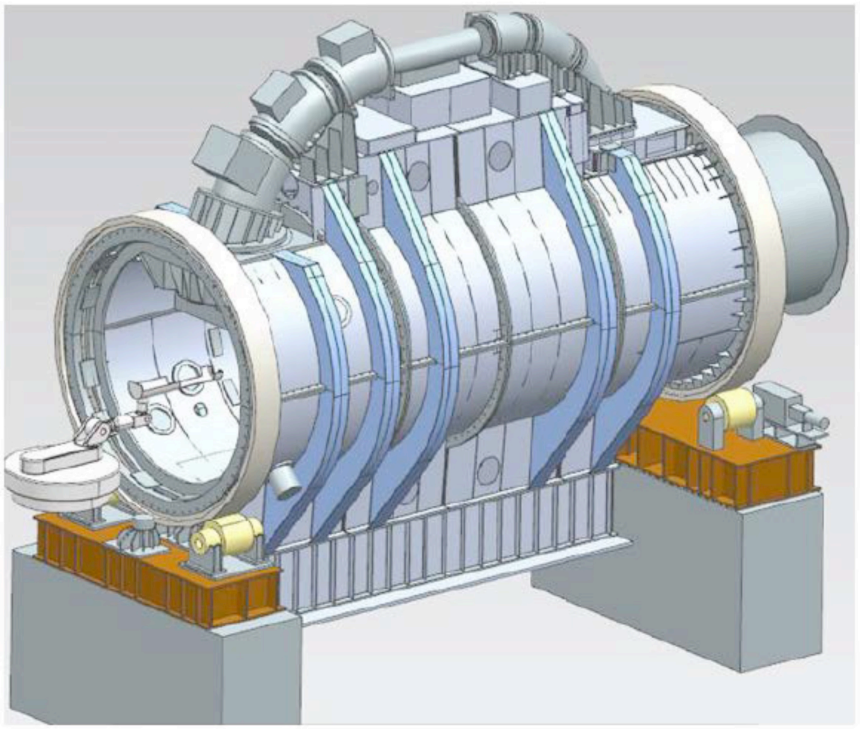

Fig. 15: The 430 MeV/u superconducting gantry built for the CHIBA centre is 15 m long and has a diameter of about 6 m. It weighs about 300 tons.

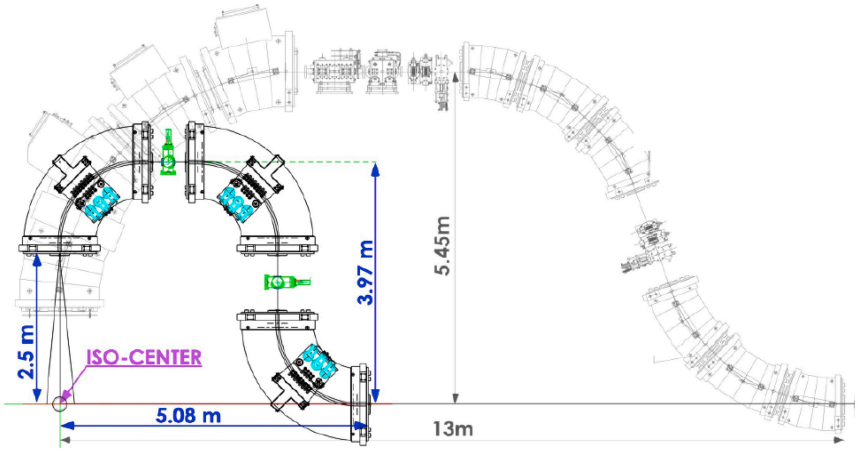

Fig. 16: The future Japanese 'compact' superconducting carbon ion gantry is compared with the gantry that is presently treating patients at CHIBA.

1.5.4 Beam monitoring and moving organs

The beam monitoring system consists of a set of position sensitive detectors and beam intensity detectors. In the existing facilities, beam position is measured using either multiwire proportional chambers (MWPC) or multistrip ionization chambers, having a sub-millimetre spatial resolution for the position of a pencil beam. As a consequence of the high scanning speed and in order to allow for multiple measurements per beam spot, a high repetition rate of about 10 kHz for these position measurements is required. For beam intensity measurements, ionization chambers are used, also with a correspondingly high repetition rate. Two independent detectors for position and intensity measurements, respectively, are used to achieve redundancy, which is required as part of the safety system: only when both detectors give consistent results does the irradiation continue, otherwise, the treatment is interrupted.

The treatment of moving tumours, e.g., liver or lung tumours, is particularly challenging with active beam delivery systems, as the combination of beam movement and target movement can lead to undesired interference patterns and consequently to distortions of the dose distribution. The development of adequate motion mitigation techniques is in the focus of intensive research and development activities, and different concepts such as gating, rescanning, and tumour tracking are being discussed. Although tracking, which is the following of the target movements by appropriate continuous adjustments of the beam deflection (with the scanning magnets) and of the beam energy, seems the most elegant way, the particular challenge here is the accurate detection of the actual target position. Therefore, gating (i.e., the treatment only during well-defined motion phases) and re-scanning (i.e., multiple irradiations with consequential wash-out of the potential distortions) are the alternatives used at present.

1.5.5 Measurements of the dose distributions: in-beam PET and prompt gammas

In order to fully exploit the advantage of the steep distal dose fall-off that can be achieved with ion beams, accurate knowledge of the beam range is of great importance. Range calculations are based on CT-image information that allows considering the differential tissue-dependent stopping power. As the corresponding calibration, as well as patient positioning and organ movement, contribute to uncertainties in the range, in-beam determination of the actual beam range during treatment is highly desirable for verification purposes. Within the pilot project performed at GSI, these measurements were done based on the positron emission tomography (PET) technique, exploiting the fact that a small fraction of the primary ions are converted into positron emitting isotopes due to nuclear reactions when the beam penetrates tissue [5,6]. The detection of prompt gammas, which are also emitted in these nuclear reactions, has been discussed for many years as a potential alternative; the first clinical instruments are now entering the clinic [7,8].

1.6 Patients treated with protons and carbon ion beams

Over the last two decades, particle beam cancer therapy has gained a huge momentum. Many new centres have been built, and many more are under construction (Fig. 17). At the end of 2016 there were, worldwide, 67 centres in operation and another 63 are in construction or in the planning stage. Most of these are proton centres, 25 in the USA (protons only), 19 in Europe (of which 3 are dual centres), 15 in Japan (of which 4 are carbon and 1 dual), 2 (1 carbon and 1 dual) in China, and 4 (protons only) in other parts of the world. The detailed characteristics of the 10 carbon (and sometimes proton) facilities are given in Appendix A.

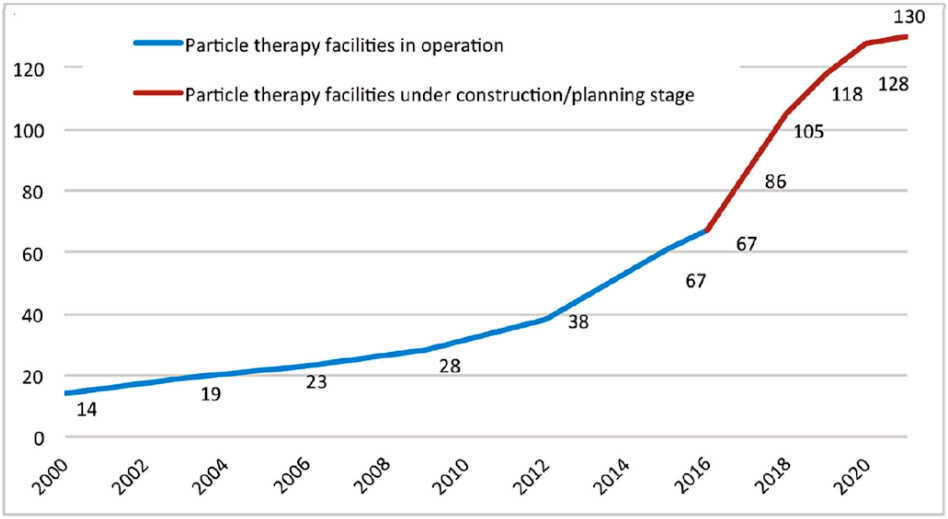

Fig. 17: Hadron therapy facilities in operation worldwide, under construction and in the planning stage at the end of 2016 (www.ptcog.com).

From 1994, when at HIMAC (NIRS) the first patient was treated with carbon ions, NIRS has been leading the development of carbon ion therapy. As discussed above, HIT was the first hospital based dual centre in Europe (Fig. 4). This was followed by CNAO in Pavia (Fig. 10) and MedAustron in Wiener Neustadt (Fig. 11). Recently the Marburg ion therapy centre has also been opened to patient treatment under the management of the HIT team.

At present sixty-three new centres are under construction so that, by 2021, there will be hadron therapy in 130 centres operating in 30 different countries. The locations of the European centres are shown in Fig. 18.

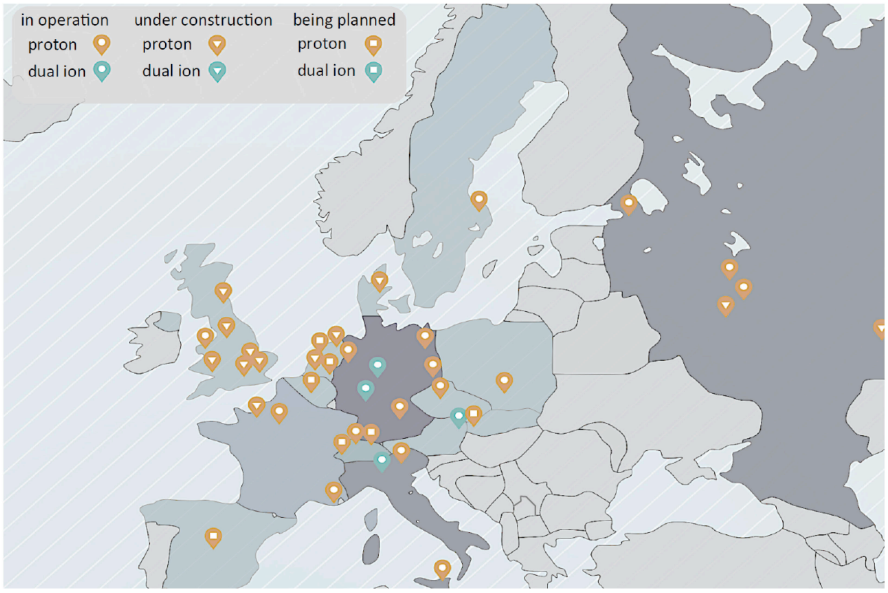

Fig. 18: European hadron therapy facilities in operation or under construction in 2016.

As shown in Fig. 19, the growth in the number of treated patients is almost exponential. At the end of 2007 the number of patients was 58,500, of which 54,000 were treated with protons and 4,500 with carbon ions. At the end of 2016 the number had grown to 168,000 (145,000 with protons, 23,000 with carbon ions). This is due primarily to the greater availability of centres, although until recently, very few randomized studies had been initiated to compare the results of hadron therapy with conventional X-ray therapy.

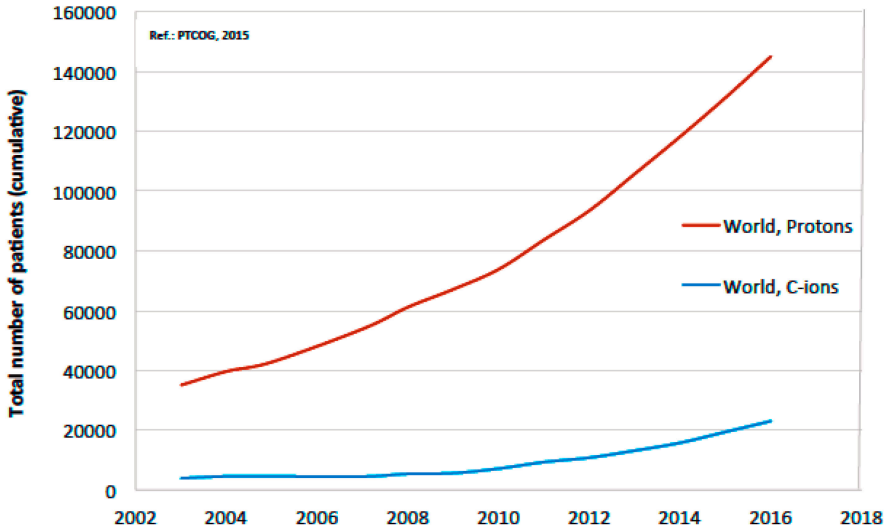

Fig. 19: Patients treated with protons and carbon worldwide by the end 2016.

Fortunately, the situation is changing, as shown in Appendix B where the on-going phase three studies are listed, and in a few years an even faster increase in the number of treated patients is expected.

1.7 Clinical programme and its equipment

1.7.1 General framework

Given the evolution of treatment techniques in particle therapy as in X-ray photon therapy, it is necessary that the equipment of the Centre, or of the nearby hospital, make it possible to achieve at least the following performance and operations:

(i) in the nearby hospital(s) supportive care and the associated treatments;

(ii) volume imaging capability in the Centre: X-ray scanner, mandatory MRI and PET scan if possible;

(iii) customized personal positioning devices;

(iv) IGRT 3D repositioning in the treatment rooms;

(v) treatment by several beams in the same position of the patient, thus having at least two different incidences (H + V or H + O or H + V + O or gantry);

(vi) dose rates which allow the rapid treatment of moving tumours in pencil beam scanning with rescanning (also called 'repainting'), i.e., rates in the range 3−10 Gy / min (for 500 mL) so that a treatment session takes less than 30−45 minutes, including installation and repositioning of the patient;

(vii) availability of several particles: protons, helium ions, carbon ions and others, as discussed in Section 1.4;

(viii) proximity of one or several housing facilities with a capacity of reception of the patients with light medical needs;

(ix) local significant capabilities to manage controlled clinical studies;

(x) local facilities for scientific visitors and groups of students or professionals for training sessions.

Treatment capacity must be defined according to the health objectives that will be given to the centre. If it is an offer of care intended to satisfy all the particle therapy needs of a given population, it is possible to show that a single treatment room can cover the needs of a population of 5 to 10 million inhabitants.

1.7.2 Types of tumours to treat and their epidemiology

The following table is based on European epidemiological studies preliminary to the Italian, Austrian, and French carbon therapy projects. This makes it possible to establish a census of priority cases for this type of therapy [9−11]. In the future, the epidemiology will have to be corrected for the age distribution of the regional population.

The cases eligible for hadron therapy account for about 10% of all radiotherapy patients, which are about 25,000 patients per 10 million inhabitants. About 1% out of this 10% is in the very first level of priority, as indicated in Table 1.

They correspond to about 280 tumours per year (80 for protons and 200 for carbon ions) for a population of ten million people, so that the Facility, treating (when completed) about 500 patients per year, will offer a cutting-edge state of the art treatment for often hopeless tumours to about two thirds of the regional population. Recruiting them will be one of the main challenges of this initiative.

In Table 1, for proton therapy the hypothesis is a significant reduction of toxicity and, for ion therapy, the hypothesis is a gain of 20% to 25% of tumour-progression-free survival, increasing the success rate from ≈ 50% to > 75%.

Table 1: Proton therapy and ion therapy indications of the highest priority.

Types of tumour eligible with highest priority for proton therapy	**Types of tumour eligible with highest priority for ion therapy (carbon)**
Adult skull base tumours.	Adenoid cystic carcinomas of salivary glands, including head & neck and thorax, sinus adenocarcinomas.
Adult unresectable or relapsing meningioma.	Mucinous melanomas of head and neck, chordomas, and chondrosarcomas of skull base and spine.
Other rare adults' central nervous system tumours.	Soft tissue sarcomas of low and medium grade, unresectable or partially resectable without threatening metastasis.
Child central nervous system tumours.	Non-small cell lung carcinomas, of small and medium size (N0,M0) unsuitable for surgery.
Any other child solid tumours.	Pelvic local relapses of adenocarcinomas, M0, and previously irradiated by X-rays.
	Hepatocarcinomas unique and of large size.
Total: about 80 cases/year for 10 million inhabitants	**Total: about 200 cases/year for 10 million inhabitants**

The second priority indications are shown in Table 2.

Table 2: Indications of secondary priority for light ions therapy.

Sarcomas after definitive R1 resection (+ children).
Lung carcinomas of medium size unsuitable for surgery.
Prostate adenocarcinomas locally aggressive.
Head and Neck locally advanced squamous cell carcinoma.
High grade gliomas (+ children).
Gastro-intestinal tumours highly radioresistant or anatomically difficult (some pancreatic tumours, pelvic tumours….).
Skull base meningiomas, unresectable.
etc.
Total: > 500/y cases for 10 million inhabitants

For the carbon ion cases listed in Table 2 the approach is essentially based on the identification of tumours anatomically either difficult to treat with X-ray and/or are radioresistant.

Concerning proton therapy, the scope of the application is less well defined because it depends on three things: the level of quality of the competing X-ray offer (for tumours with difficult anatomical localization), the existence or not of an offer of light ion treatments, which is also competing (for radioresistant tumours), and, finally, the economic resources that can be allocated to a costlier therapeutic modality such as proton therapy. Taking these parameters into account, the demand for proton therapy can range from one to three or even fourfold compared to the demand for

light ions. Thus, one can count on 200 to 800 cases of first and second priority proton therapy for 10 million inhabitants per year, considering almost all the children to be treated for curative purpose[‡‡].

As a whole, it can be emphasized that for most of the cases it is a question of rare tumours, the recruitment of which, in order to obtain a particle-therapy decision, presupposes a healthcare system that is efficient and able to handle all types of cancers and to cover the entire population in an equitable manner.

1.7.3 Practical organization of treatments: logistics and recruitment, follow-up

The Clinical Network of oncology departments of hospitals, located inside and outside the Region, will have to be organized to cover the geographical area drained by the particle-therapy centre of SEE. The hub of the Network is better placed in an already well-equipped conventional radiotherapy department located in a different country, so as to involve, even before the beginning of the Facility, as many centres as possible.

This Network should organize the identification of eligible cases, the systematic and traceable discussion of these cases in a collegial and multidisciplinary centralized tumour board, if possible in the form of a single weekly teleconference meeting to apply the same selection criteria in all participating centres. This work will have to be done downstream of the local multidisciplinary tumour board meetings which will have the role of proposing a radiotherapy orientation for the eligible cases. Definitive eligibility will be devoted to the special network centralized tumour board. Of course, the Network will be also responsible for the multicentre clinical studies discussed in the next subsection.

All eligible patients who will accept the possibility of being treated by hadron therapy, and possibly be part of a study, will have to be seen in full consultation with their entire medical file by a radiation oncologist specialized in particle therapy, either in one of the regional centres of the Network or in the central Facility. Just after this consultation, the patient, who will generally come from a distance, should be able to have the first session of his/her care at the Centre, in particular the realization of a personalized positioning device followed by an imaging session in the treatment position. This can take a day and therefore justifies the need for a housing capacity nearby.

The patient then returns home for the treatment preparation period, of approximately two weeks, and then comes and stays on site for the duration of the treatment. This duration can be very variable: from a week, for a very hypo-fractionated treatment, up to 7 or 8 weeks for currently fractionated proton therapy. As a reminder, the reference time for a carbon ion treatment is currently 4 weeks for 16 successive fractions, at a rate of one fraction per day, 4 to 5 days per week. Proton therapy requires more fractions. Anyway, the patient, and often also a relative, have to be lodged in a housing not far from the Facility.

At the end of the treatment, as with any oncology patient, patients will have to follow a surveillance programme (follow up) by one of the centres of the Network that can last from 5 to 10 years, or even more for certain endpoints related to very late toxicity. In fact, it is impossible, for reasons of medical availability and of travelling costs, to centralize all of the follow-up activity in the Facility. Oncologists or specialists in the vicinity of patients should therefore carry out most of the follow up. Nevertheless, it is useful for the development of the medical expertise of radiation oncologists of the hadron therapy centre to be able to follow some of these patients for a certain length of time. So it will be necessary to find a way to do so. This may depend on various criteria: patient will, place of residence, possibility of displacement, particularity of the case, etc.

Since today virtually no hadron therapy is part of an irrefutable standard of care, it is important, and even necessary, for any patient to participate in one way or another in the scientific evaluation of particle therapy.

[‡‡] Institut Curie-Paris, private communication.

1.7.4 Multicentre clinical research and local clinical research

The current development of particle therapy in Europe, with about twenty proton therapy centres and four carbon therapy centres, makes possible the establishment of multicentre prospective clinical studies. ESTRO and ENLIGHT work together to achieve this. All multicentre studies should be able to be activated in this future hadron therapy centre.

It could then be assumed that the acceptance of a patient to be definitively eligible for a hadron therapy, paid by a health insurance, should be conditional on his/her inclusion in a trial that would correspond to his/her type of tumour, or, at least, his/her inclusion in a follow-up cohort. This principle includes, of course, randomized comparative studies comparing hadron therapy versus X-ray therapy, which creates the situation of having no hadron therapy for half of the recruited population.

This principle being laid down, it must be recognized that, in particular in paediatrics, no comparative clinical studies have been carried out and many indications of proton therapy in paediatrics are considered by many to be accepted standards. In adult situations, even for indications considered validated in proton therapy, the question of the comparison of carbon therapy versus proton therapy arises. As a result, any adult should be able to participate in a clinical research protocol. In the absence of protocol adapted to the condition of truly eligible patients, patients should participate in at least a cohort follow-up protocol with a long-term prospective collection of monitoring data: tumour response, tolerance and quality of life in the very long term, second cancers, etc. This can be done through Internet applications specifically developed for patients. The collection of these data must imperatively be carried out in all cases. This is mandatory in any protocol of clinical trial and this should be organized in personalized or cohort follow up for all patients who would not be included in a prospective clinical trial. So practically one should learn something from 100% of patients.

1.7.5 Equipment for the clinical programme

As stated in Section 1.1, the goal is to treat 500 patients in 50% of the daytime. Since in a treatment room working full time one can treat 250 patients/year, the completed Facility will feature four treatment rooms:

(i) one room with a horizontal beam;

(ii) one room with a horizontal and a vertical beam;

(iii) a proton gantry;

(iv) a light ion gantry.

To devote 50% of the daytime to the clinics, patients' treatments will begin in the early mornings and end in the late morning or early afternoon, and this for 5 days per week.

To reduce the initial financial commitment, it is foreseen that initially only the first two rooms will be equipped and that the proton gantry and the ion gantry will be added in subsequent phases. Most probably the bunkers will have to be constructed from the beginning.

1.8 Radiobiology programme and its equipment

1.8.1 General framework

To fully utilize the beneficial radiobiological properties of ion beams, a concerted research effort is called for providing enhanced knowledge on the tumour resistance mechanisms and on the methods to identify them, at the time of the diagnosis, in order to help clinicians in their decision making for treatment. Systematic radiobiological data to give guidance to the biologists and physicists on how to properly apply and improve the potential capabilities of particle therapy are also needed.

This need is widely recognized in the community but existing centres do not have sufficient beam time available for the required basic research efforts. Their focus is on clinical use, and research time is often limited to a few hours at a time, not adequate for systematic research studies. Thus, the

international hadron therapy community urgently needs a dedicated centre for radiobiology research and physics research, offering extended blocks of beam time, with beams of a variety of ions and energies suitable for multidisciplinary clinically oriented research. The SEEIIST Facility will respond to this need by providing a range of different ion species (from protons to argon ions) for systematic radiobiology experiments to better characterize the relative biological effectiveness (RBE) and its complex dependencies, allowing also improvements of the biophysical models that are required to implement these dependencies in the treatment planning procedures.

1.8.2 In vitro and in vivo radiobiology: open problems

The radiobiological background for hadron therapy has been described in Section 1.2-1.4. While the physical properties of these radiations have been the aim of intense research, less focus has been put on the actual biological responses to cell irradiation.

The radiobiological response to hadron radiations is on many levels different from that of photon radiation [12]. Data for determining clinically relevant RBE values are of great importance, but it should also be emphasized that the biological effects of particle radiation is not for all endpoints a question of a dose effect that can be corrected with a RBE factor, but is rather seen as a different biology [13]. To fully exploit the advantages of particle therapy, there is a range of unresolved radiobiological questions that must be answered, and there is a need for more experimental in vitro and in vivo radiobiological data to support and elaborate on the existing knowledge.

As the time frame for the proposed project is not yet defined, it is difficult to envisage which research topics will be of highest interest at the time when the beams will become available in the experimental halls. At present it is sufficient to list some of the most important topics which are currently under investigation, demonstrating that research in this field is still of the utmost importance despite the fact that clinical facilities are already in operation:

(i) An increased proton RBE at the end of the particle range is clearly visible in in vitro studies, but in clinical settings this seems to play a less pronounced role. Therefore, the debate is ongoing as to whether the increased RBE at the distal edge of a treatment field needs to be considered in treatment planning for proton therapy. To close the gap between in vitro and clinical studies, in vivo studies are indispensable for a better understanding of the above-mentioned discrepancies.

(ii) Due to the better conformation of the dose, partial volume effects might play a more important role in ion beam therapy; as typically small volumes are involved, these might counteract the locally increased effectiveness. This interplay between partial volume and RBE effects also requires in vivo studies, as partial volume effects cannot be mimicked by in vitro systems.

(iii) There is increasing evidence that radiation treatment in combination with a stimulation of the immune system might further increase the effectiveness of the treatment. Also, modulation of the repair capacity in combination with radiotherapy might be beneficial. Systematic studies on all such types of combination treatments are required.

(iv) Stem cells are at the origin of normal tissue regeneration and also represent the major players for the regrowth of tumours after radiotherapy. A better understanding of the peculiar properties of stem cells with respect to radiosensitivity, repair, and regeneration capacity is of high importance for the improvement of any radiation treatment modality.

(v) Drugs, nanoparticles and other agents can modify the radiation response and thus the bio-effectiveness of radiotherapy. There are many open avenues since only a small fraction of the possible choices has been experimentally studied.

(vi) Cell migration represents one of the key processes leading to metastases. The problems to be tackled are: how far radiation can either enhance or reduce the ability of cells to migrate and

affect the occurrence of metastases and whether there are differences in that respect between sparsely and densely ionizing radiation.

(vii) Treatment planning for ion beam therapy requires the use of biophysical models. Although a lot of experimental data are already available, discrimination of different models should be optimized using experimental conditions that are particularly sensitive to model differences and thus frequently require additional experimental data.

(viii) As conformity of the treatment is much better with ion beam irradiation, at the same time reducing the volume and/or dose to the normal surrounding tissue and thus normal tissue complications, other factors like the probability of secondary cancer induction will become an important factor for the choice of the optimal treatment modality.

Systematic studies at all levels from in vitro cell transformation up to secondary cancer induction in animal models are thus desirable to better characterize the essential differences between conventional and ion beam treatments. Considering also other research directions like radiation protection or more fundamental studies to elucidate the mechanisms of radiation action, a plethora of further topics can be envisaged which would fit into a research programme of such a facility.

1.8.3 Reference radiation source

For RBE studies there will be a need for a reference radiation source. Traditionally, ^{60}Co has been used as reference, but most facilities have phased-out ^{60}Co irradiation, and most radiobiological studies are now using X-rays as a reference. For X-irradiation of small animals there are specific advanced X-ray units available, such as the cabinet X-Ray irradiator (220−250 kV) produced by Precision X-ray (PXi, Connecticut). However, it has to be kept in mind that using orthovoltage X-ray as reference radiation, rather than the more clinical relevant megavoltage, is already introducing a slightly differential biological effect. Indeed, orthovoltage X-rays have a LET slightly higher than the one of megavoltage X-rays.

1.8.4 Equipment for the radiobiology programme: low-energy line

The samples are placed in magazines of approximately 20 samples below the beam line and are taken by a vacuum grab to move it in the beam for irradiation (see Fig. 20).

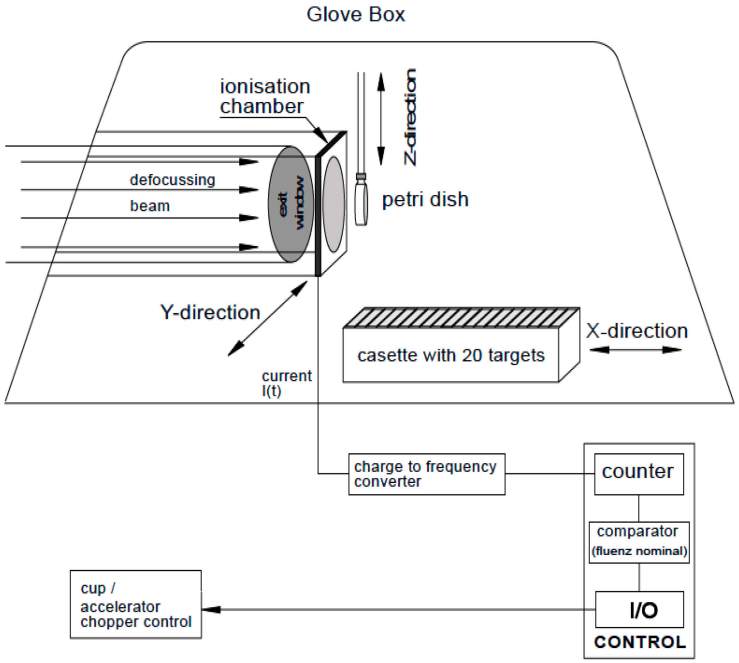

Fig. 20: Schematic view of the low-energy beam line sample changer, as it is used at the UNILAC beamline at GSI, Darmstadt.

In vivo biological experiments at the low-energy beam line require energies of 7−10 MeV/u, depending on the ion species. This minimum energy is defined by the energy loss in the exit window (thin, about 20 micron hostaphan/kapton), the thickness of the ionization chamber required for dosimetry and small air gaps that are technically required to allow irradiation of standard cell culture vessels e.g., Petri dishes, flasks etc.

No scanning system is required here, as radiobiological experiments at low energies typically use broad beam irradiation with no specific requirements concerning complex field geometries. The typical field sizes can be kept comparably small (about 5 cm diameter). Widening of the beam by using ion beam optical elements like quadrupoles will be sufficient; this helps to keep the cost for this additional beam line to a minimum.

Dosimetry is performed using a thin ionization chamber, which is calibrated by means of CR39 track detectors that are irradiated exactly at the position of the biological samples. Homogeneity checks can be visually qualitatively performed using a scintillation screen. By analysing the spatial distribution of particle tracks on the CR39 detectors one can obtain a quantitative validation.

Samples are irradiated in air, i.e., the medium flows out of the Petri dishes as soon as the samples are lifted from the magazine to the irradiation position. Only a very thin medium layer remains, covering the cells and preventing cells from drying for several minutes.

A control system can be realized using off-the-shelf industrial components and software development environments like e.g., LabView, etc.

An example for the layout of such an irradiation facility is shown in Fig. 21. As the setup is contained in a closed box (this is required for biological safety reasons), it can be easily removed and replaced by other devices like e.g., an online microscope, setup for materials research etc.

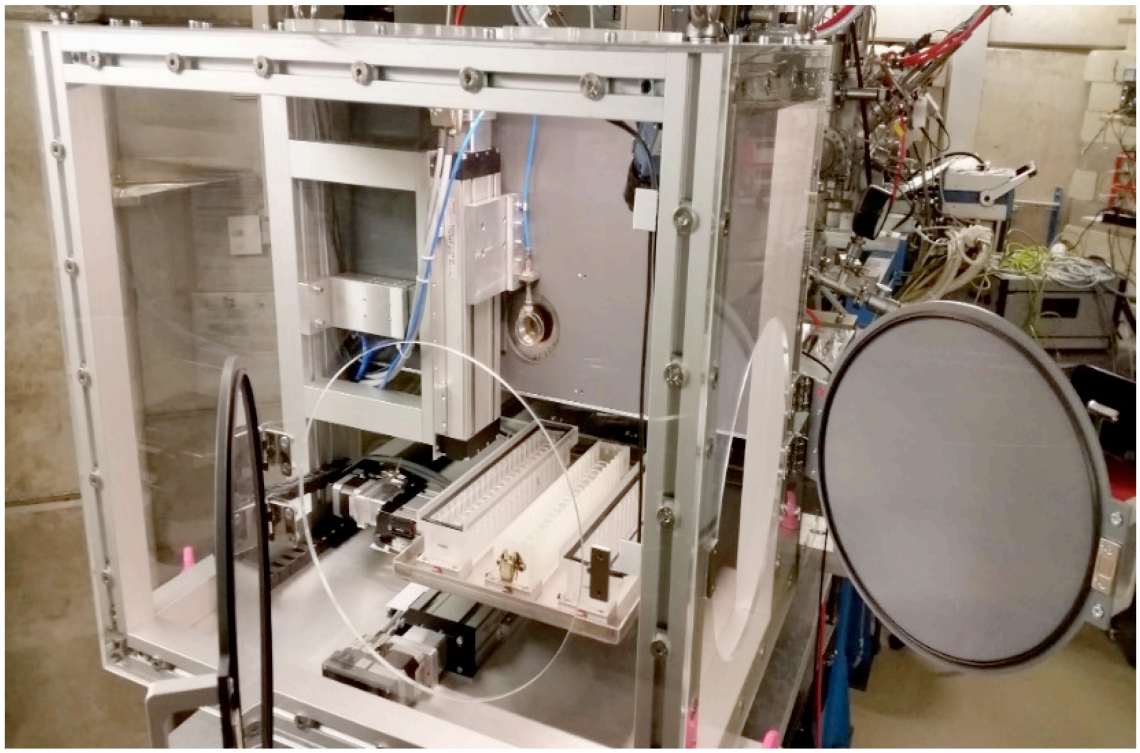

Fig. 21: Photograph of the new sample changer setup, as it is used at the UNILAC beamline at GSI, Darmstadt.

1.8.5 Material science

As mentioned in Section 1.1 and detailed in Appendix D, the low-energy beam can also be used for experiments on materials. The main fields of research are:

(i) *Ion beam analysis* (IBA), which includes a series of analytical techniques with MeV ions in order to probe the composition, elemental depth profile, local chemistry, and structure of solids.

(ii) Material modification, in which MeV ions induce pronounced modification of the structural, physical, and chemical properties of a given material.

(iii) Radiation hardness studies, in which ion beams are used for testing the radiation hardness of materials used for nuclear waste storage or of electronic components, in particular in space applications.

1.8.6 Equipment for the radiobiology programme: high-energy line and target handling

The beam delivery for the experimental cave for radiobiology experiments must have the same flexibility as the patient treatment rooms, i.e., it must be equipped with a fully active 3D raster scan system and the corresponding monitor system. The minimum field size for radiation biology experiments is about 10×10 cm^2.

Reducing the redundant system layout, i.e., using only one position sensitive and one intensity sensitive monitor chamber, could minimize costs. In addition, the interlock system could be designed in a simpler way, depending on the type of validation experiments that should be performed in the experimental cave.

To reduce the needed investment, initially one could also envisage performing critical experiments directly in the patient treatment room and reserve the experimental room only for less demanding experiments. Attractive solutions could consist of a hybrid system, combining of an active lateral 2D scanning system with a range shifter that allows scanning the beam in depth. This solution requires only a few pre-set mono-energetic beams to be prepared for the experimental room.

As passive depth scanning produces a slightly higher contribution of fragments in the beam, it should be carefully discussed which level of accuracy and comparability to the fully active 3D beam delivery is required. Comparisons between the passive system at HIMAC with the active system at GSI, however, revealed that differences are marginal if other conditions - in particular width and depth of the *spread-out Bragg peak* (SOBP) - are identical [14].

For standard irradiation with comparably small SOBP even simpler solutions can be implemented, using 3D-ridge filters [15] that allow for substantial reduction of irradiation times, thus increasing sample throughput.

Application of simple rectangular fields with mono-energetic beams does not require the use of a complex treatment planning system; the control system thus should allow using a 'bypass' of the typical patient-like delivery procedures based on a separate simple, robust, and fast software module for this task. For the more patient-like biological experiments, however, the full chain should also be available starting with the plan generation using an experimentally oriented *treatment planning system* (TPS) procedure.

As a consequence of the higher beam energy and more sophisticated beam delivery system much higher flexibility is given with respect to sample types and target geometries. Most experiments can be performed using standard culture flasks (12.5, 25, or 75 cm^2), but also e.g., phantoms, in which biological samples are spatially distributed, can be used or any other more complex geometry by exploiting the capabilities of the scanning beam delivery system.

For standard experiments, a robust sample handling system is needed that allows for high-throughput experiments which optimally utilize the available beam time and are then mostly limited by the irradiation time per sample. Simple moving belts have been helpful e.g., at the GSI facilities, where up to 10−15 samples can be placed in a row and irradiated sequentially without the need for access to the treatment room (see Fig. 22).

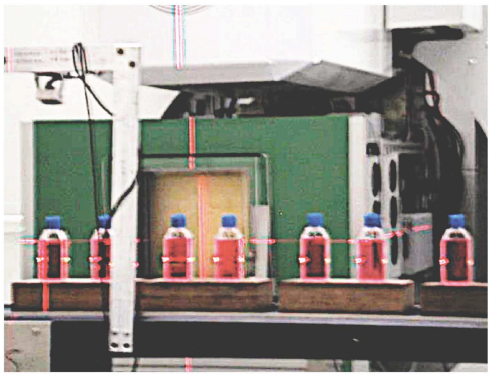

Fig. 22: Conveyer belt system used at GSI.

1.9 Animal programme and its equipment

1.9.1 General framework

As mentioned in the last section, in hadron therapy there is a surprising lack of data from in vivo experiments, which in other treatment modalities have been regarded as a necessary link between the hypotheses generated by in vitro experiments and patient treatments. Cell experiments give good indications of the various effects, but in reality, in vivo, there are many biological functions interacting together, which is impossible to mimic in vitro.

To be able to comply with the issues of a different radiobiology and a varying RBE in hadron therapy, it is crucial to have experimental biological studies to determine the extent and magnitude of these effects. As a necessary next step, from in vitro studies, in vivo studies enable simulation of clinical treatments in animal models and give essential information to determine the optimal radiation modality to protect normal tissues and to optimize the anti-tumour effects. The possibility of devoting ample times to these studies, on various in vivo models, makes the Centre unique in the world landscape.

1.9.2 Problems to be faced

At present, one of the crucial points in particle radiobiology is to establish the RBE of different normal tissues in a systematic, large-scale in vivo setup, using relevant particles. This should include simulation of clinical treatment with fractionation as well as different positions in the beam. Relevant normal tissue models should include functional and tissue endpoints, representing both early and late radiation induced reactions.

The list is long; however, a number of examples can be given with some relevant bibliography:

(i) assays for acute skin reactions [16] and radiation induced fibrosis [17] (Fig. 23);

(ii) models of neurological damage of the spinal cord, central nervous system, peripheral nerves, optic nerve, etc. [18];

(iii) lung injury [19];

(iv) urinary bladder function [20];

(v) cartilage tolerance;

(vi) different tissue types and position of the irradiated organ along the beam path and the SOBP;

(vii) cognitive assays, such as *novel object recognition* (NOR) and *novel object location* (NOL) [21];

(viii) dose fractionation.

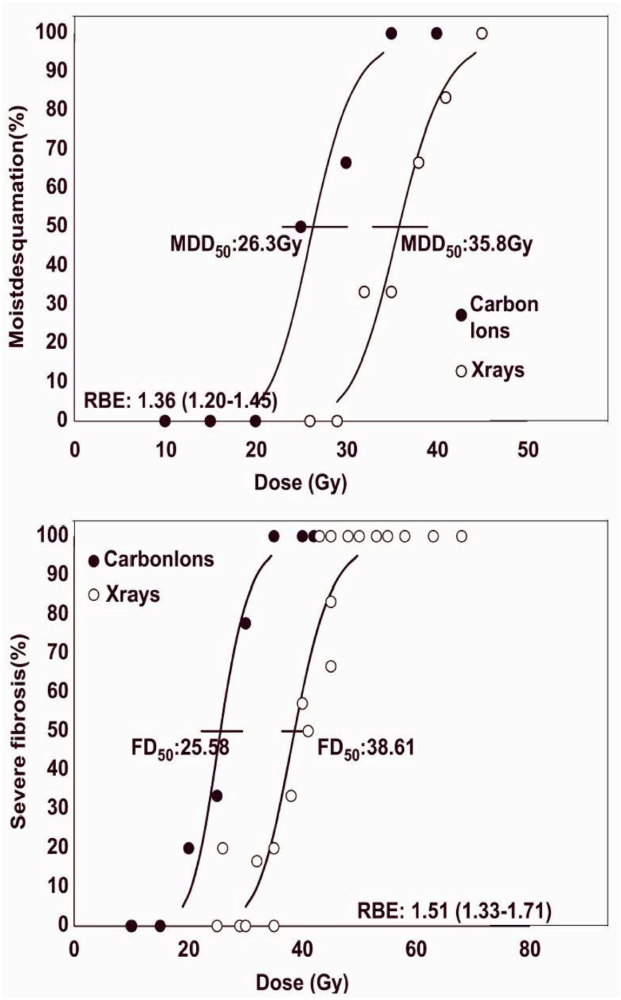

Fig. 23: Examples of in vivo data on early and late radiation induced reactions. Here from acute skin reaction (moist desquamation of irradiated areas of the skin) (top panel) and radiation induced fibrosis, a late reaction of tissue to radiation (lower panel), in carbon ion irradiated mice [22].

The normal tissue studies should be accompanied by in vivo studies of RBE of a panel of tumours' models with different radio sensitivities to enlighten the therapeutic effect at different LETs.

In addition to these compulsory RBE studies, question as what impact high LET radiation has on factors as cytokine expression, inflammation, and angiogenesis have been raised, and suggestive data from both in vitro studies [23−25] and clinical studies [26] have suggested a differential effect from photon radiation. However, to elucidate whether these effects could possibly have a clinical effect, in vivo studies are needed.

As animal models are not trivial to set up in a facility, an animal study programme could be partly based on researchers from other institutions, where animal models have already been implemented, refined, and optimized.

Projects could use animals that stay temporarily at the facility for irradiation, and are then brought to the home institutions for follow up, as this can be a very long process; for late reactions, the time for observing the animals can be up to several months or years.

1.9.3 Programme of the animal experiments

As discussed above, the variation of RBE and the possible clinical impact thereof will be investigated in a systematic, large-scale setup using a panel of clinically relevant in vivo models.

To conduct the experiments an in-house animal facility will be established for permanent housing of small rodents. Larger animals will be treated in collaboration with an external academic veterinary department.

This long-term activity will provide data for the development, in collaboration with the other European institutions, of biological models and their implementation in human treatment planning systems. Finally, such a high-quality preclinical research is necessary to secure solid foundations for clinical research.

1.9.4 Equipment for animal experiments

An example of a small-scale, yet complete and self-sufficient, animal facility for small rodents is shown in Fig. 24. The Centre will feature a small animal facility similar to the one shown in this figure. Besides this, a cleaning room for washing equipment, as well as a laboratory will be available.

It has to be considered that there are legal requirements for the building specifications for an animal facility, e.g., of the noise level, on ventilation, and temperature. It has to be approved for housing of experimental animals by the authorities. All facilities for housing and treatment of animals will comply with EU regulation.

For a part-time facility, based on a visiting scientist bringing their own equipment, the animal facility should contain one or more conditioned cabinets for small rodents (as a Scantainer or similar). The animal facility should, as a minimum, be equipped with a laminar flow for animal handling. There should be access to a range of general laboratory equipment, but this could be done in connection with a possible in vitro facility.

The animal facility should be in close proximity to the experimental beam room to avoid too long transport between animal preparation and animal treatment. A possibility would be to place the animal facility in the basement, with direct connection to the experimental beam room, to avoid patient areas to be exposed to allergens.

Larger animals could be brought to the site only when needed, and then the follow up could be done in an external facility.

If a setup with a visiting scientist with visiting animals is considered, it is necessary to have an isolated section that can serve as the quarantine room for a temporary medical physics programme and its equipment housing of animals, to ensure no risk of contamination between visiting and in-house animals.

1.10 Medical physics programme and its equipment

1.10.1 General framework

From the medical physics point of view, the success of a tumour treatment depends both on the accuracy of the treatment plan and on the quality, precision and reproducibility of the detectors, which control and ensure that the distribution of the delivered dose is equal—within an accuracy of about 2%—to the optimized output of the *treatment planning system* (TPS).

With about 25,000 patients treated worldwide with carbon ions, even though the amount of accumulated knowledge is impressive, many areas are still almost uncharted, in particular since the medical community is now moving towards the use of ions different from carbon atoms. Many ion species will be available at the Centre, which will have both the instrumentation and the beam time to study them.

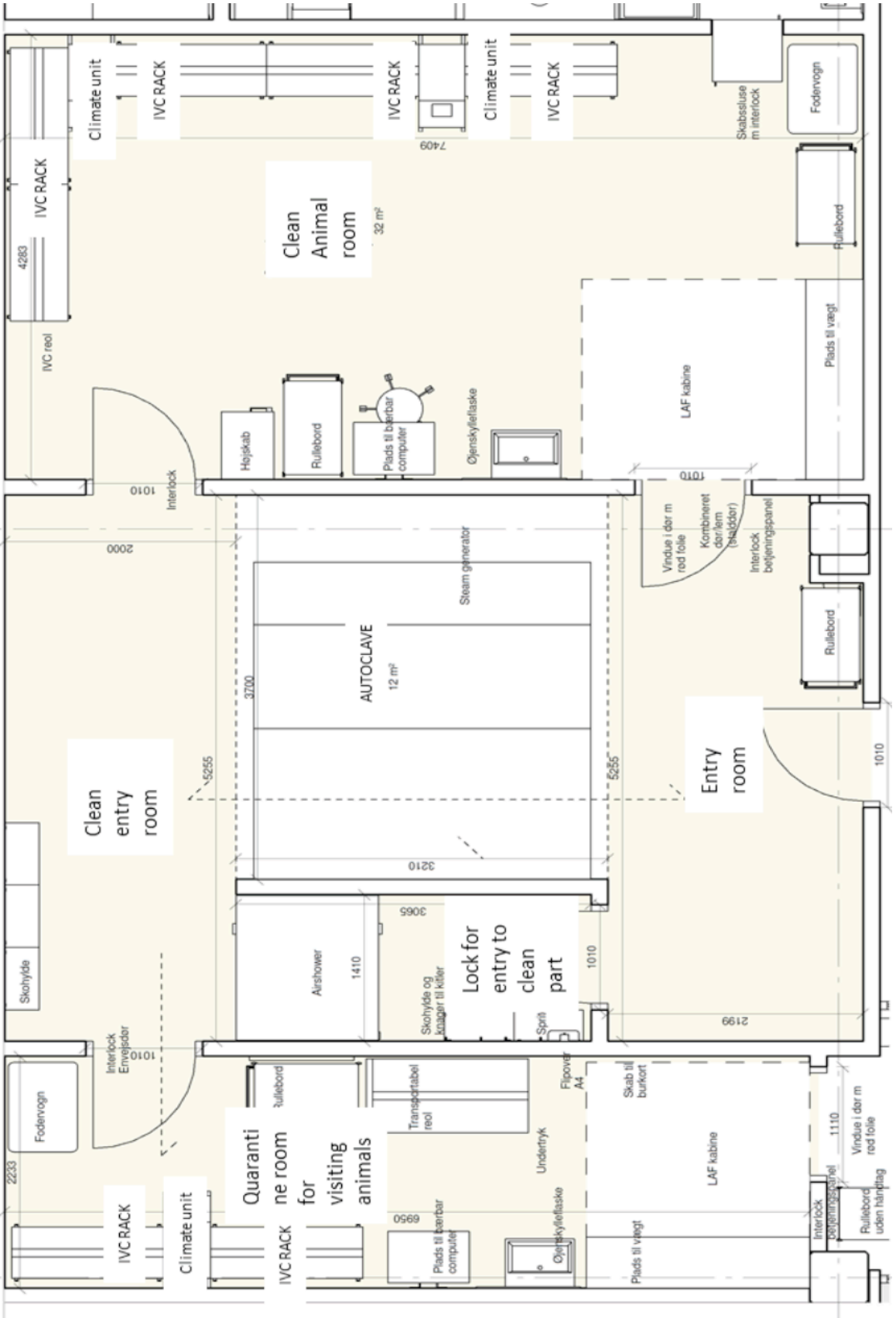

Fig. 24: Schematic of the newly designed animal facility for small rodents at the Department of Experimental Clinical Oncology, Aarhus University Hospital.

1.10.2 Medical physics programme

To fully expand the therapeutic application of particle beams, there is a range of physics questions that need to be solved, in close collaboration with the other European and Japanese centres, in order to:

(i) Measure very accurately the stopping power of living tissues by new imaging modalities as for example 'proton radiography' (tomography).

(ii) Measure the fragmentation of the different ion species, in biological matter. The results will be implemented in Monte Carlo-based TPSs, to enhance the accuracy of the range calculation and fragmentation related dose.

(iii) Develop new beam monitors detecting, during and after the treatment, and with millimetre accuracy, the position where the ion beam stops in the patient body to assess, in real time, the accuracy of the dose deposition. This is at present centred on the detection either by PET of isotopes produced in the interactions of the ions with the body nuclei, or of 'prompt gammas', which are also emitted in these nuclear reactions secondary to fragmentation, but other techniques are being developed such as proton radiography and ultrasounds emitted by the beamlet interacting with tissues.

(iv) To track moving organs and provide a 3D localization in space of a tumour that moves during the treatment. Many techniques are being developed but none are currently fully satisfactory; this will be certainly one of the focus of the experimental activity.

As a whole, many technological achievements will come out and better detectors will be developed and brought from the laboratory to the clinic and industry.

1.10.3 Equipment for the medical physics programmes

The physics experiments will be performed in the Facility experimental hall(s) at the end of dedicated transport lines. At least one of these horizontal lines will have the possibility of transversally scanning the beam on an area of at least 15 cm × 15 cm.

In principle it would be possible to share the beam(s) with the in vivo and in vitro programmes, but the preferred solution is to have from the beginning different beam(s) in the same experimental hall. As a later stage, a second experimental hall will be built to widen the potentialities of the Facility and of its experimental programmes.

To develop and qualify some detectors, measurements will have to be conducted also in the treatment rooms on either phantoms or patients. These experiments will greatly profit from the very special feature of this Facility, i.e., the fact that only about 50% of the daily day time will be devoted to patient treatments.

1.11 Two extended networks

To reach the clinical and scientific goals two networks will have to be setup from the beginning of the project and continuously extended. It would be convenient to locate the hubs of these two networks, as well as the veterinary department for large animals, in countries that are different from the one in which the Facility will be built. This will make the best use of all the expertise in the Region and facilitate the approval of the overall project.

The Clinical Network, discussed in Section 1.7, should be the first one. It will give the opportunity to the hospitals and oncological institute*s* of the Region to work together, even before the construction of the Facility, and, afterwards, to refer patients to the Facility and share clinical prospective investigations and patient follow up. Secondly, it will allow the radiation oncologists of the Region to work together with their European colleagues (in particular at HIT, CNAO, and MedAustron) and non-European colleagues in multicentre prospective comparative studies to improve the knowledge both in hadron therapy and in classical radiation oncology through clinical research practice.

This Network will need a wide bandwidth connection to exchange medical records and images so that all involved experts will participate in regular teleconferences gathering to review and discuss patient cases for medical decisions; this is a powerful tool for professional development and training, data sharing, and referral to the Facility of the patients who need hadron therapy treatment.

The second network is a Scientific Network of universities, research centres, and hospitals, which will connect all the groups either doing or planning to perform experiments in the experimental halls of the Facility. Also, in this case the hub of the Network should be located in an institute of a different country than the one in which the Facility will be built and the main collaborators will be at HIT, CNAO, and MedAustron. The ensemble will work as one of the large international collaborations that build instruments and perform experiments at the CERN accelerators. Indeed, all the scientists and medical doctors will have the same purpose: performing their experiments in optimal conditions and, at the same time, utilizing at best the beam time made available at the Facility. In the framework of this Network a Programme Committee, composed of experts both internal and external to the Facility, will allocate the beam time.

1.12 Education and Training

The primary objective of this initiative is not only to extend existing research activities and treat patients but also to create completely new opportunities for cutting-edge research and technology for the welfare of the Region.

Secondly, it is the hope that by struggling and working together for a common task, the human relations between scientists and engineers as well as between administrators and politicians from countries with different and sometimes problematic histories can be an essential element in building mutual trust, as has been successfully demonstrated by the cases of CERN and SESAME.

Training of the young generation is an essential and integral part of the initiative. The realization of the projects will take several years, which gives sufficient time to train not only the team that will help to build and later operate the installations, but also to form a user community. In both cases, specialized users in the important fields that will be served by the facilities do not yet exist in the Region and have to be created. This will be an essential part of capacity building.

The training will mainly consist of two parts.

The first is to grant fellowships for young people to be sent to European laboratories for one or two years to get education and training as scientists or engineers in various special fields. The management of such a programme would be the task of the project leaders by selecting promising candidates from the Region and finding host laboratories to host them.

The second component of training would be the organization of workshops and schools for future users. These should be organized by a Training Programme Committee to be set up from the beginning.

More specifically, before time zero, at least one year, probably two years, will be devoted to educating and training the people coming from the Region, who, under the leadership of a few world-known experts, will constitute the core group of the construction team that will design, build and commission the Centre. These young engineers and scientists will be trained by the European institutes, which will take the responsibility to help and support, in the long term, the project.

After this initial period, the two networks described in Section 1.11 will be used to gather the necessary expertise and training the new experts coming mainly from the Region. This training will be done by having the personnel of the Facility both visiting foreign centres for long stays and following courses that will be given, by internal and external teachers, on site. Indeed, one of the main goals of the Facility is to train highly competent experts in numbers, which exceed the needs of the Facility, so that other hospitals and institutions will eventually employ them, thus raising the cultural level and the quality of the work done in the Region.

The Facility will be very naturally linked to the universities of the Region and will be an excellent partner for Master and PhD courses and theses.

1.13 Knowledge transfer and spin-offs to the Region

Technology and know-how transfers are vital parts of the initiative.

In order to attain the goals, the accelerator and the high-tech hardware and software components of the complex will not be ordered as a unit from industry but, rather, will be designed, with the help of experts and laboratories in Europe, and will be built, mounted, and commissioned by the construction team. This is the usual way in which most scientific laboratories have been created in Europe. Only conventional equipment would be bought off the shelf from industry whereas, for new developments, prototypes will be ordered and later production contracts will be awarded to industry. This allows for a large flexibility in the use of the most modern technologies for the projects and, as experience has shown, provides an extremely efficient technology transfer to industry. It also reduces the total cost of the projects since the global risk is not placed on the shoulders of industry. To facilitate the collaboration with industry it is envisaged that a kind of 'training programme' for and with industry will also be established with the task of explaining to firms not yet in contact with research institutions how to cooperate and how to present proposals for adjudication of contracts.

With the construction of this Facility there will be many opportunities for technology transfer to the SEE countries. First, the procurement of the different components for the machine and beam lines (magnets, vacuum system, girders, beam lines, power supplies, control system, etc.) can be preferentially assigned to local industries. Wherever the capabilities of local industries are lacking it will be conceivable to establish joint R&D programmes for pre-series prototypes, thus promoting these industries. These prototypes should be manufactured in the member countries by giving their industry a special education/training from other facilities and from the staff of the Centre. With the production of the prototypes, the home industries will be formed to be successful in a later call for the tendering process. Likewise, it will be necessary to educate the industries to bid successfully following the procurement rule of most advanced EU countries.

Like the training programme, we believe that the technology know-how transfer programme outlined could help in creating a set of skilled scientists who will be attracted to work at the Facility and no longer seek employment elsewhere in Europe, thus reversing or alleviating the brain drain suffered by the Region.

The initiative will give rise to spin-off activities not directly linked to the facilities but providing an initial spark for new activities in the Region. Two examples may be mentioned. The Facility will need electric power that will be a non-negligible part of the operating cost. To reduce this, one could consider installing solar panels. This cannot be considered only for the Centre, since power is needed also when the sun is not shining; on the other hand, power can be supplied to the general network when the accelerator is not working. Hence such an option must be integrated in the regional power network.

A second spin-off development concerns the creation of regional broadband-digital networks. The two networks described in Section 1.11 will serve a large user community that is spread out in the Region and Europe. The infrastructures needed to transmit data from the Centre to the users, and vice versa, might become a model for a wider network for the Region, much as the World Wide Web created for the users of CERN has attained worldwide importance.

2 Conceptual design of a multiple-ion therapy and research centre

2.1 Choice of the study case

The second part of this report is devoted to the description of the facility—which is needed to pursue the goals, as described in the first part, in tumour therapy, radiobiology, animal studies, and medical physics—and to its cost estimates.

Since for costing the synchrotron and the transport beam lines it is necessary to choose a specific design, it has been decided to use as a case study the PIMMS design described in Section 1.5, which has given birth to CNAO and MedAustron (Figs. 10 and 11). It has to be underlined that the decision to study this case does not imply that this design will be chosen for the construction of the South-Eastern European Facility.

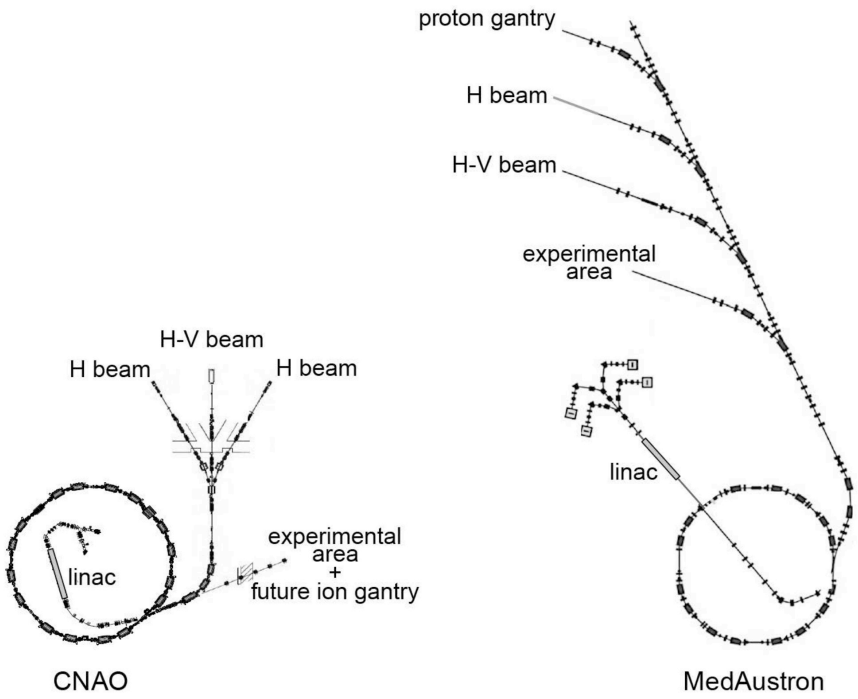

Fig. 25: Comparison of the layout of the two facilities built on the basis of the Proton and Ion Medical Machine Study held at CERN between 1995 and 2000.

2.2 Overview of the accelerator system

The layout of the accelerator system is based on the 25-metre diameter PIMMS synchrotron of Fig. 26, which can accelerate different types of hadron beams, such as helium, carbon, oxygen, neon, or argon, and is suited for many research programmes, such as those discussed in the first part, and for treating tumours.

The facility features three sources, but more can be added, and three high-energy beams, which are only indicative of what can be done to distribute the beams to the various areas discussed in Section 2.6. The hadron beams are generated in an *electron cyclotron reso*nance (ECR) ion source.

A *low-energy beam transport* magnetic line (LEBT), with spectrometer magnets for ion separation, is connected to the ion source. The LEBT beam is matched to the input of a *radio frequency quadrupole* (RFQ) which accelerates the beams from 8 keV/u to 400 keV/u. Subsequent acceleration is performed with a sequence of two drift-tube linacs up to a beam energy of 7 MeV/u.

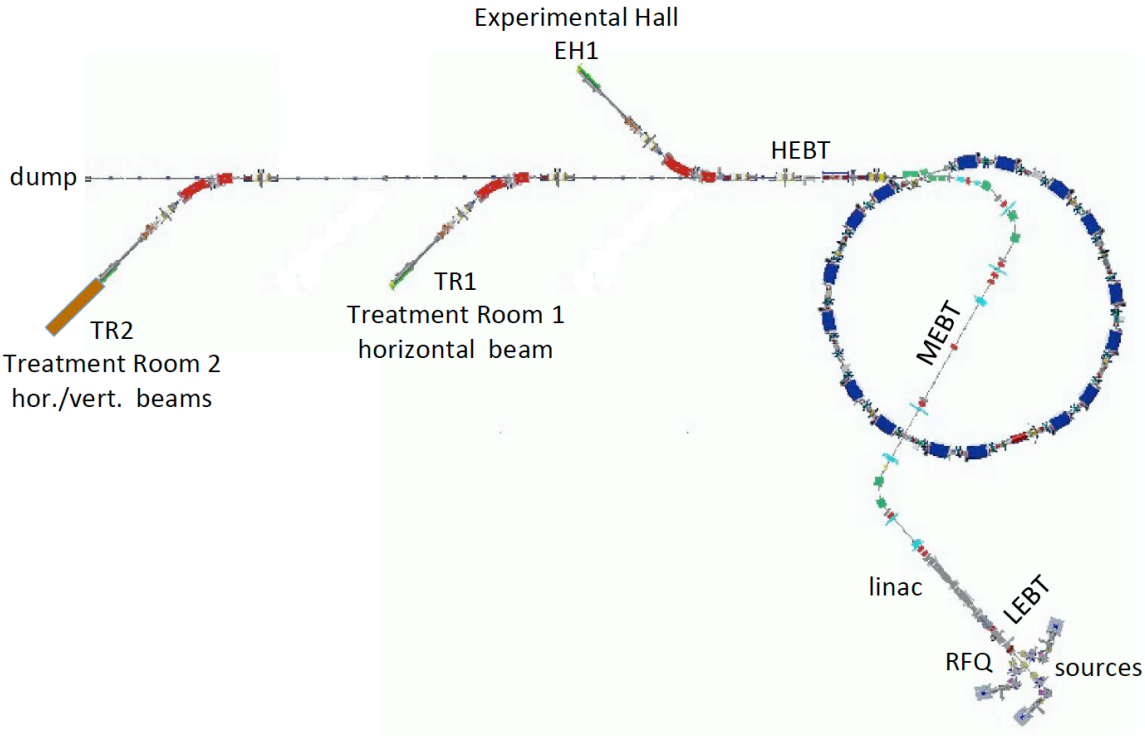

Fig. 26: In the basic layout of the accelerator system there are three sources and three beamlines, one of which is straight and guides the particles to a beam dump.

A *medium energy beam transport* line (MEBT) strips, de-bunches, and charge-state separates the beam and transports the selected ions to the injection point of the synchrotron. A multiturn injection is performed in the synchrotron to provide the required intensity.

The synchrotron accelerates the beam to the requested energy and stores it for subsequent slow extraction. A *high energy beam transfer* line (HEBT) transports the beam either to the experimental area or to a treatment room.

The layout of Fig. 26 has three beamlines, the first to the right toward an experimental area for research purposes (EH1), the second and the third to the left toward two patient treatment rooms (TR1 and TR2). Of course, there is the possibility of modifying the distribution and use of the lines and of adding new ones. The proposed layout is described in Section 2.6.

The dimensions and numbers of magnets are given in Table 3.

Table 3: Dimensions and numbers of magnets for the basic system of Fig. 26.

Approx. dimensions of accelerator with one treatment room	
Circumference of the synchrotron	77.6 m
Length of the injector (LEBT, linac, MEBT)	≈ 60 m
Number of magnets (linac not included)	162
Number of magnet power supplies (linac not included)	130

In the next sections the different components of the system are described. The technical specifications of the different parts are given in Table 4, following the beam path from the source to the patient.

Table 4: General specifications of the particle accelerator system.

Ion species	Symbols and values
Beam particle species	$^{4}He^{2+}$, $^{12}C^{6+}$, $^{36}Ar^{16+}$, (with proper setups all species between p and Ar can be accelerated, in particular p, O, Ne.)
$^{4}He^{2+}$ energy range [MeV/u]	(30-) 75-220[a]
$^{4}He^{2+}$ range [mm]	(9-) 45-300
$^{12}C^{6+}$ energy range [MeV/u]	(50-) 140-430[a]
$^{12}C^{6+}$ range [mm]	(7-) 47-310
$^{36}Ar^{16+}$ energy range [MeV/u]	205-352
$^{36}Ar^{16+}$ range [mm]	30-74
$^{36}Ar^{18+}$ energy range [MeV/u]	205-430
$^{36}Ar^{18+}$ range [mm]	30-102
Maximum number of He ions per spill	$\geq 10^{10}$
Maximum number of C ions per spill	$\geq 10^{9}$
Maximum number of $^{36}Ar^{16+}$ ions per spill	$\geq 2\ 10^{8}$
Maximum number of $^{36}Ar^{18+}$ ions per spill[b]	$\geq 2\ 10^{7}$
Setup Change	
Time to change between ion sources	≈ 1 min
Time to switch beam from room to room	≈ 1 min
Time between end and start of extraction for new acceleration cycle.	< 2 s
Ramping time of synchrotron to highest magnetic field	< 1 s
Beam intensity variation with respect to maximum number	0.01-1
Stability of extracted beam	
Beam intensity instability (100 ms averaging time and Dynamic Intensity Control activated; the first 100 ms of spill are not included).	< ±5%
Extracted beam intensity fluctuations (averaging on 1 ms)	Max/Min < 5
Beam width variations at isocentre	< 20%
Integral intensity variation without Dynamic Intensity Control activated	< ±30%
Average energy variations from synchrotron	< 0.1%

[a] Energy range within which beams are compliant with clinical specification. For beams with energies between the lower clinical energy limit and the energy in parenthesis, clinical beam quality is not guaranteed.

[b] For $^{36}Ar^{18+}$ lower intensity can be provided because of the low stripping efficiency.

2.3 From the ion source to the synchrotron extraction system

2.3.1 Injection line

The ECR ion sources can be operated either in DC or in pulsed mode. The beam current is reproducible within ±5% from beam cycle to beam cycle. The parameters are listed in Table 5.

Table 5: Source parameters for some ions used for hadron therapy.

Ion type	$^{1}H^{+}$	$^{4}He^{2+}$	$^{12}C^{4+}$
Ion current (μA)	700	1000	200
Energy (keV/u)		8	24
Ion source potential (kV)	24	16	24

Each ion source branch of the LEBT is equipped with a solenoid, a quadrupole, two horizontal and vertical correctors, a 90-degree spectrometer dipole magnet, and a quadrupole triplet.

The purpose of the LEBT beamline is to select the ion type of interest (with a mass-to-charge ratio (*A/Q*) in the range 1.0 to 3.0), to transport it and to match the beam to the acceptance of the RFQ located downstream of the LEBT. In order to clean the desired ion beam from atomic, molecular, or isotopic impurities, the ions are filtered by a magnetic spectrometer system, which has a resolving power of more than 50. Moreover, to cut the needed portion of beam injected in the RFQ, an electrostatic chopper system generates pulses n of a few hundred microseconds, as required for the pulsed operation of the linac. At the end of the LEBT a linac system accelerates the ions to the injection energy. The linac system consists of three linear accelerators: a RFQ (up to 400 keV/u) and two IH (Interdigital H-type) drift tube structures (up to 4.2 MeV/u and 7 MeV/u respectively). The linac is pulsed at 5 Hz with a pulse length of 0.3 milliseconds and has a peak power of 250 kW. The total peak power is about 1.1 MW. The linac system has a transmission in excess of 70%.

The MEBT beamline transports the 7 MeV/u beam from the linac to the injection point of the synchrotron. It contains a stripper foil, which strips and possibly dissociates the beam to fully stripped atomic ions (except for argon ions for which full stripping to bare nuclei has prohibitively low yield), separates the ion species depending on their mass-charge ratio and, with an RF cavity, debunches the beam and hence reduces its energy spread.

2.3.2 Synchrotron

The lattice is based on two symmetric, achromatic arcs ($m_x = m_z = 360°$ with bending angles equal to 180°) that have been de-tuned and joined by two dispersion-free straight sections (Fig. 27).

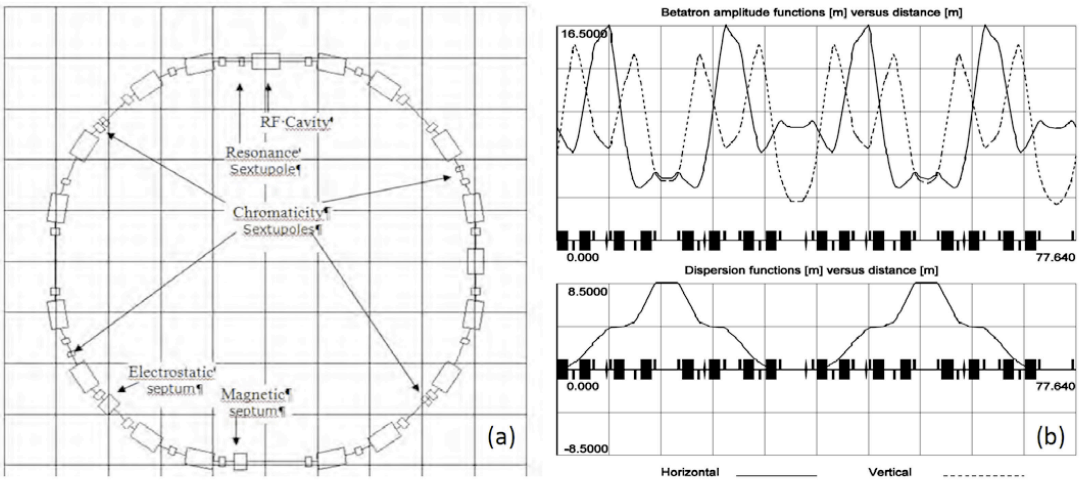

Fig. 27: (a) Geometry of the synchrotron that features 16 bending magnets, 24 quadrupoles, and 4 sextupoles. (b) Optical functions: betatron functions (above) and dispersion (below).

The beam from MEBT is multiturn injected into the synchrotron to obtain an increase in the current from the linac by a factor of five.

The beam is subsequently accelerated to the requested energy in less than one second. After acceleration, the beam is slowly extracted during up to 10 s with high efficiency. For gating operation, the duration of the high-energy flattop can be increased up to 30 s. The main specifications of the synchrotron are listed in Table 6.

Table 6: Main specifications of the synchrotron.

Injection/Acceleration	**Unit**					
Particle after stripping		p	$^{4}He^{2+}$	$^{12}C^{6+}$	$^{16}O^{8+}$	$^{36}Ar^{16+}$
Energy	MeV/u	7	7	7	7	7
Magnetic rigidity at injection	Tm	0.38	0.76	0.76	0.76	0.86
Acceleration rate	Tm/s	10	10	10	10	10
Ramp-down time of magnets	s	< 1	< 1	< 1	< 1	<1
Lowest extraction energy	MeV/u	60	75	140	120	205
Highest extraction energy	MeV/u	220	220	430	430	352
Magnetic rigidity at lowest extraction energy	Tm	1.14	2.54	3.53	3.25	4.88
Magnetic rigidity at highest extraction energy	Tm	2.42	4.52	6.62	6.62	6.62
Maximum number of particles per spill		$2 \cdot 10^{10}$	$1 \cdot 10^{10}$	$1 \cdot 10^{9}$	$5 \cdot 10^{8}$	2.10^{8}
Momentum spread	%	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Extraction time	s	1-10	1-10	1-10	1-10	1-10
Spill pause length	s	0.1 - 20	0.1 - 20	0.1 - 20	0.1 - 20	0.1 - 20
Spill structure, intensity ratio I_{max}/I_{min} (average on ≥1 ms)		< 5	< 5	< 5	< 5	< 5

The 24 quadrupoles are grouped in three families that allow enough flexibility to match all the needed tunes while conserving the dispersion free regions. The four chromaticity sextupoles are grouped in 2 logical families and are placed such that it is possible to change independently the horizontal and vertical chromaticity; these magnets are individually powered to allow some additional flexibility in setting up the extraction.

Extraction is performed by RF-knock out at multiple energies during the same accelerator cycle, a procedure abbreviated as EVE that stands for ‘energy variable extraction’. After an extraction EVE allows the acceleration (or deceleration) in about 100 milliseconds of the remaining particles to a different energy, so that the system is ready for another extraction without loss of beam quality. This procedure reduces the irradiation time when the dose to be deposited at a certain energy requires small number of particles.

2.4 Beam transfer to the treatment and experimental rooms

In the basic layout of Fig. 26 the HEBT line transports, with small losses (<5%), the beam from the synchrotron to 2 therapy rooms and 1 experimental room. The optics system allows at the isocentre adjustable sizes of 5−15 mm FWHM (Full Width at Half Maximum), as shown in Table 7. The

experimental beamline has a double isocentre: one for a conventional field size (20×20 cm^2), and the other, after a longer drift, with an enlarged field size (40×40 cm^2).

Table 7: Main specifications of the HEBT line.

Adjustable beam width (FWHM) at isocentre for protons and helium ions at max energy (mm)	7-10-15
Adjustable beam width (FWHM) at isocentre for carbon ions at max energy (mm)	5-8-10
Transverse field for scanning in the treatment rooms (cm^2)	20×20
Transverse fields for scanning in the experimental area (two positions) (cm^2)	40×40

The HEBT starts with the magnetic extraction septa and contains a common beamline and two beamline branches to the beam ports of the rooms. Each branch begins with a 45° bend realized as a pair of a 15° and a 30° dipole magnets powered by one power supply. The experimental line is pointing in opposite direction with respect to the first treatment line. This layout allows the design of a flexible experimental area with multiple rooms and configurations to accommodate different research projects.

Table 8: Main specifications of the HEBT line.

Maximum transverse scanning speed (m/s)	20
Distance from scanner magnets to isocentre in the horizontal and semi-vertical beamlines (m)	7.4
Momentum spread (95%), $\Delta p/p$ (%)	<0.1
Dispersion at isocentre, D (m)	<0.1
Dispersion gradient at isocentre, dD/ds	<0.1

The common part of the HEBT line contains a beam abort system, which prevents any beam particles entering the beamline within 200 μs after an interlock signal. It consists of two corrector magnets with a deflection angle of 6 mrad on both sides of a fast switching magnet with a deflection angle of 12 mrad at the centre. Extraction can also be stopped by switching off the RF power going to the KO (knock-out) exciter. The beam extraction can be resumed using the RF KO-exciter. The time needed to abort and resume extraction is about 1 ms.

2.5 Software

2.5.1 Control System

The main task of the control system is to load the many processors, which are on board of the different devices, with the relevant settings, depending on the planned cycles to be executed, and to monitor the achievement of the planned results.

The areas covered by the control system are the following:

(i) distribution of the events to synchronize the behaviour of all the devices;

(ii) generation or choice of the set points to be used in each cycle by the devices;

(iii) generation and visualization of the information to monitor the treatment;

(iv) execution of the tasks to prepare the plant to the treatment execution;

(v) execution of the tasks to verify the correct behaviour of the plant;

(vi) implementation of the plant safety system;

(vii) execution of the tasks that allow placing the patient in the right position;

(viii) execution of the tasks to deliver the beam on the target with the right amount of dose.

Fig. 28 shows the conceptual architecture of the Control System.

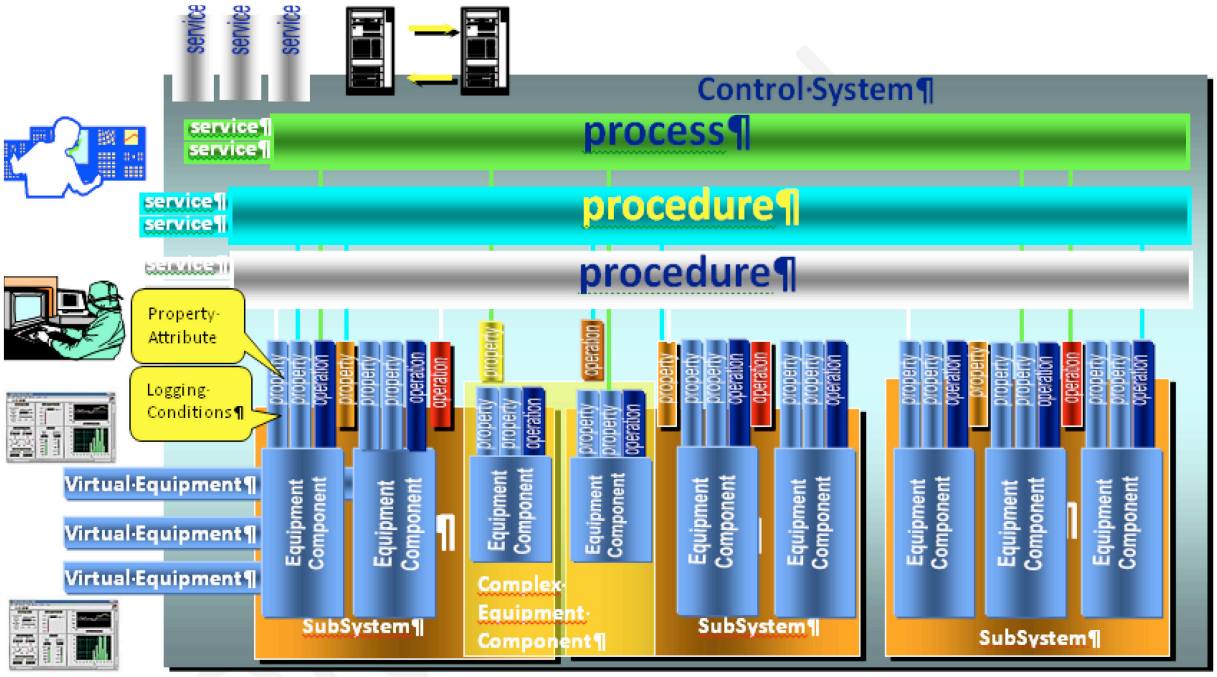

Fig. 28: Software architecture of the Control System.

The concepts presented above are translated into a layered architecture based on a network of dispersed processors. Each layer has a set of specific tasks to be accomplished to supply services to the immediately upper level or to the operators.

Fig. 29 shows the main components of the conceptual layered architecture.

2.5.2 Dose Delivery System (DDS)

The DDS includes the acquisition data software, the interfaces with the treatment planning system, the communication interfaces with the control, timing, and safety systems. By means of the control system, the accelerator machine cycle, set by the DDS, is distributed to the accelerator components.

The DDS has the task to drive the scanning magnets currents, which define the requested position of the beam in the plan orthogonal to its propagation direction (X and Y coordinates), while the Z position of the Bragg peaks is determined by the energy of the particles.

The tumour volume to be treated is subdivided, by the treatment planning system (TPS), into several slices, located at different depths inside the patient. The DDS is able to recognize the completion of the treatment of each slice thanks to a real-time check of the beam and thanks to a monitoring of the treatment evolution.

The end of a voxel, exactly like the end of a slice, is decided by the DDS through the measurement of the number of particles, by means of two integral ionization chambers. At the end of the irradiation of the voxel, the DDS communicates to the power supplies of the scanning magnets the new beam position.

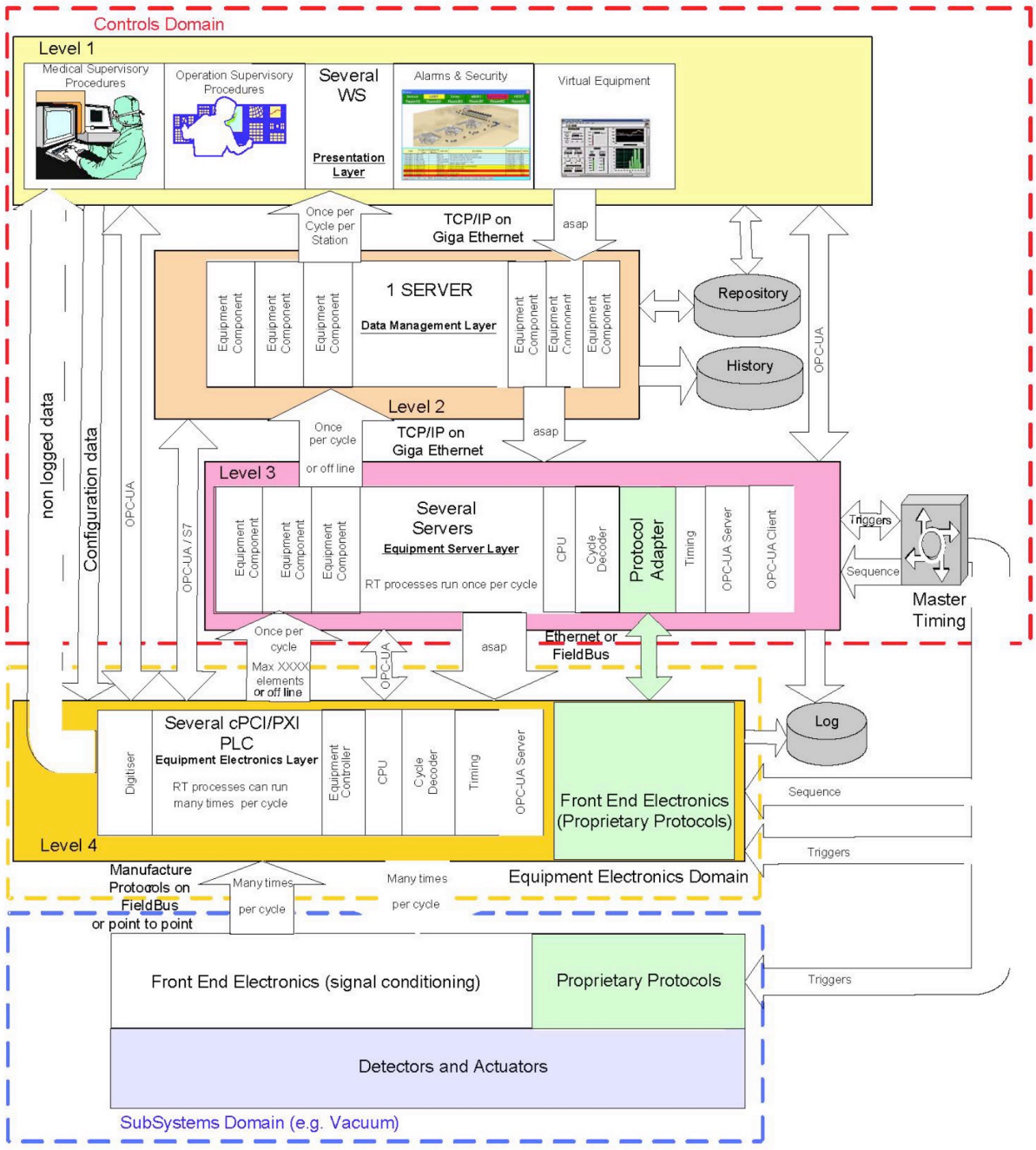

Fig. 29: Control system layered architecture.

2.5.3 Medical software and Quality Assurance tools

The medical software includes the *oncology information system* (OIS). The custom interface standard called 'DICOM Treatment Machine Interface' of the OIS gives the unique opportunity of achieving the 'Record and Verify' full connectivity within the particle therapy environment, supporting pre-treatment checks including patient positioning, treatment accessory and synchrotron setting verification, treatment delivery data, and image recording in the patient database. It includes licences for electronic medical record for radiation oncology, resource scheduling setup intelligence, DICOM (Digital Imaging and Communications in Medicine) radiotherapy ion plan import and export, connections to third-party PACS (Picture Archiving and Communication System), TPS and diagnostic scanners, sequencers for transport beamlines, and DTMI hadron delivery Treatment Planning System for ions.

A system that can be adopted is RayStation® Version 5, which represents the state-of-the-art of a modern TPS in terms of advanced patient modelling, plan design, optimization and evaluation, biological modelling for carbon ions, GPU-based pencil beam carbon dose calculation engine, treatment adaptation, scripting, and quality assurance (QA) plan preparation.

The configuration of RayStation® V5 includes licenses for each of the following modules: carbon planning, deformable, tracker, and adaptive. Advanced patient anatomical modelling, such as structure definition, image registration, propagation of structures, atlas-based and model-based segmentation, manual and semi-automatic organ and target delineation tools, is available. IMPT (intensity modulated particle therapy) optimization and *relative biological effectiveness* (RBE)-weighted dose computation using the *local effect model* (LEM) for carbon and helium ions and proton treatment plans are supported.

2.6 Staging of the project

The construction of the treatment rooms and of the experimental halls can be staged so that a relatively small initial investment will allow from the beginning significant clinical and research activities; a possible layout development is shown in Fig. 30. Note that the clinical areas and the experimental areas are on opposite sides of the HEBT line so that there is no mixing between the flow of the patients and of the scientists working in the experimental halls. The sequence of Fig. 30 is only one of the many possible scenarios. The design that will be realized will be determined by the goals of the persons in charge at the time together with the inflow and the time-profile of the necessary funds.

According to the scenario of Fig. 30, the research programmes will be carried out in two EHs halls devoted to *radiobiology* (RB), *animal studies* (AS) and *medical physics* (MP), where beams of many different ion species will be available, with the maximum energies listed above. For radiobiology experiments the Centre will feature also a low-energy beam (7-8 MeV/nucleon), produced by the injector. If the staging approach is adopted, at the beginning of the exploitation RB and MP experiments will be performed in the same hall.

The construction sequence described in the figure is as follows:

(i) The baseline design foresees three ions sources, one tumour treatment room (TT1) with a horizontal beam, one tumour treatment room (TT2) with a horizontal and a vertical beam and, given the research purposes of the facility, a large experimental hall (EH1) with 2-3 beams for in vivo radiobiology (RB), animal studies (AS) and medical physics experiments (MP). The synchrotron accelerates hadrons at the highest energies and a low-energy beam for radiobiology is produced by the linac.

(ii) In the second stage a third treatment room, with a proton gantry, can be added. The three treatment rooms (TT1, TT2 and TT3) have the same footprint so that a proton gantry (Section 1.5) could also be mounted in TT1 and TT2. The addition of two high-performance sources is foreseen to widen the research possibilities.

(iii) The addition of an ion gantry and of a third experimental hall (EH3) (Section 1.5) could complete the facility giving more scope to the clinical research programme. A sixth source increases the number of ion species routinely available at the Facility.

2.7 Site requirements

The layout of Fig. 30C covers an area of about 170 m x 90 m. At present it cannot be said whether the bunker, containing the accelerator and the beam lines, will be constructed in an underground bunker or at ground level. This will depend on the dimension of the site, the possible height limitations and the stability of the ground. Surface buildings will hosts three types of staff, those who are involved in the running of the Facility, those who will provide tumour treatments and the visiting scientists coming from collaborating Institutions and Hospitals.

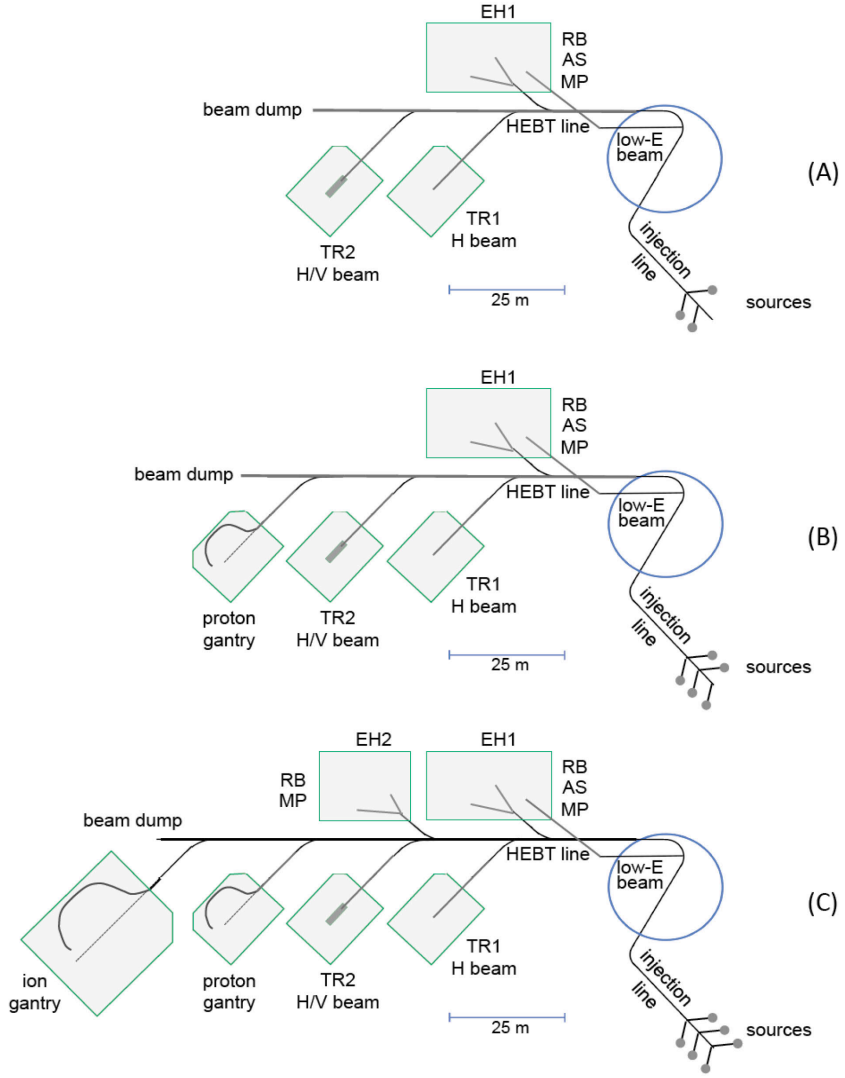

Fig. 30: Three topologies that can be used for staging the project starting from the baseline layout (layout A). The ion gantry room of layout C is so large to contain the GSI gantry (Fig. 4) but at the time of construction smaller superconducting gantries will be available (Fig. 16).

At this stage it can be said that, to cover all the needs, an area not smaller than 300 m x 180 m has to be foreseen, corresponding to twice the area of the layout of Fig. 30 C.

The electric cabin serving the facility should have a capacity not smaller than 10 MVA and the water flux for cooling the equipment should be at least 1,400 cubic metre per hour.

In the 2−4 rooms of the layouts of Figs. 30A and 30C, 250−500 patients, coming mainly from the Region, will be treated every year. Since only outpatients will be irradiated, the Facility should be built not too far from a hospital, which could provide to the patients the necessary care integrating the offer of the Hadron Facility. The presence in the hospital of a radiotherapy department, featuring modern linacs for X-ray therapy and the corresponding medical imaging tools (CT, PET, CT/PET, and MRI), would represent an important asset. This would also reduce the investments needed to install and maintain in the Facility some of the costly diagnostic tools mentioned above. In any case, the instruments installed in the Facility should complement the ones available in the nearby hospitals.

As discussed above, for programme B2 (Animal Studies) an in-house animal facility will be established for permanent housing of small rodents. The animal facility will be placed in the basement

and will have a direct connection to the experimental beam room, to avoid patient areas being exposed to allergens. The animal facility will include an isolated section which can serve as temporary housing for visiting animals, brought in by visiting scientist, and which will after treatment be taken to the home institution. This will enable the most flexible use of the experimental facilities.

Larger animals will be brought to the site when needed, on the basis of a scientific collaboration agreement with a veterinary department, which would be best located in one of the SEE countries that does not host the Facility. This department will also take care of the follow up. All facilities for housing and treatment of animals will comply with EU regulation.

As for all the facilities of this type, the roads should be such that heavy pieces of equipment can be transported and the airport should not be too far, since many scientists will visit the laboratories to perform experiments and patients, with their relatives, will have to spend on average 4−5 weeks in the Centre.

Since an average treatment lasts 20−25 sessions, at the beginning more than 20 patients will be in the treatment areas every day; this number will double when the Centre will be completed. A guesthouse and/or nearby hotels are needed to host them with their relatives.

2.8 Timeline and organization

2.8.1 Timeline

Overall 6 years will be needed: 1 year for the preparation, 4 years for the construction and on-site mounting, and 1 year for the commissioning. The training of the local staff will take 1−2 years. Construction and commissioning times are given in Fig. 31.

2.8.2 Organizational model

A complex multipurpose research Centre, as the one described in this report, cannot be ordered ‘turn-key’ from a company because the team that will commission, run, and improve it over the years has to know in detail the inner working of its parts and the reasons for the choices made during the planning, specification, construction, integration, and commissioning phases. A more effective approach foresees that the facility is designed, built, and commissioned by a group of experts together with a ‘local team’ of talented young and enthusiastic people selected among graduate and post-graduate students—with some full-time senior scientists and engineers—which will become knowledgeable under the guidance of the experts.

During the first year the management of the Institute will also have the responsibility of defining the specifications of all of its many subsystems and later, with the help of the group of experts and the active contribution of the local team, will follow their construction, on-site mounting, and acceptance tests. In the initial training and design phase the Institute will also investigate the existence and availability of local firms, possibly close to the site of the Centre, which could be involved in the facility realization. This choice has many advantages: firstly, it implies the investment of money in local firms and the creation of labour opportunities and revenues; secondly, it will allow the technology transfer to local industries that will then be more competitive on the international market; thirdly, it will induce the creation, close to the Centre, of firms that could contribute to the maintenance of the facility once in operation.

After 1−2 preparation years, devoted to the education and training of the local team members and to the definition of the detailed specifications of the facility components, the Institute will sign contracts with 2−3 ‘main contractors’, which will provide, using as much as possible Regional subcontractors, the high-tech components of the facility and will take care of their shipment and on site mounting and testing. One of these main contractors will produce, install, and test the control and safety software, the patient environment, and the integration of the two worlds, technical and medical.

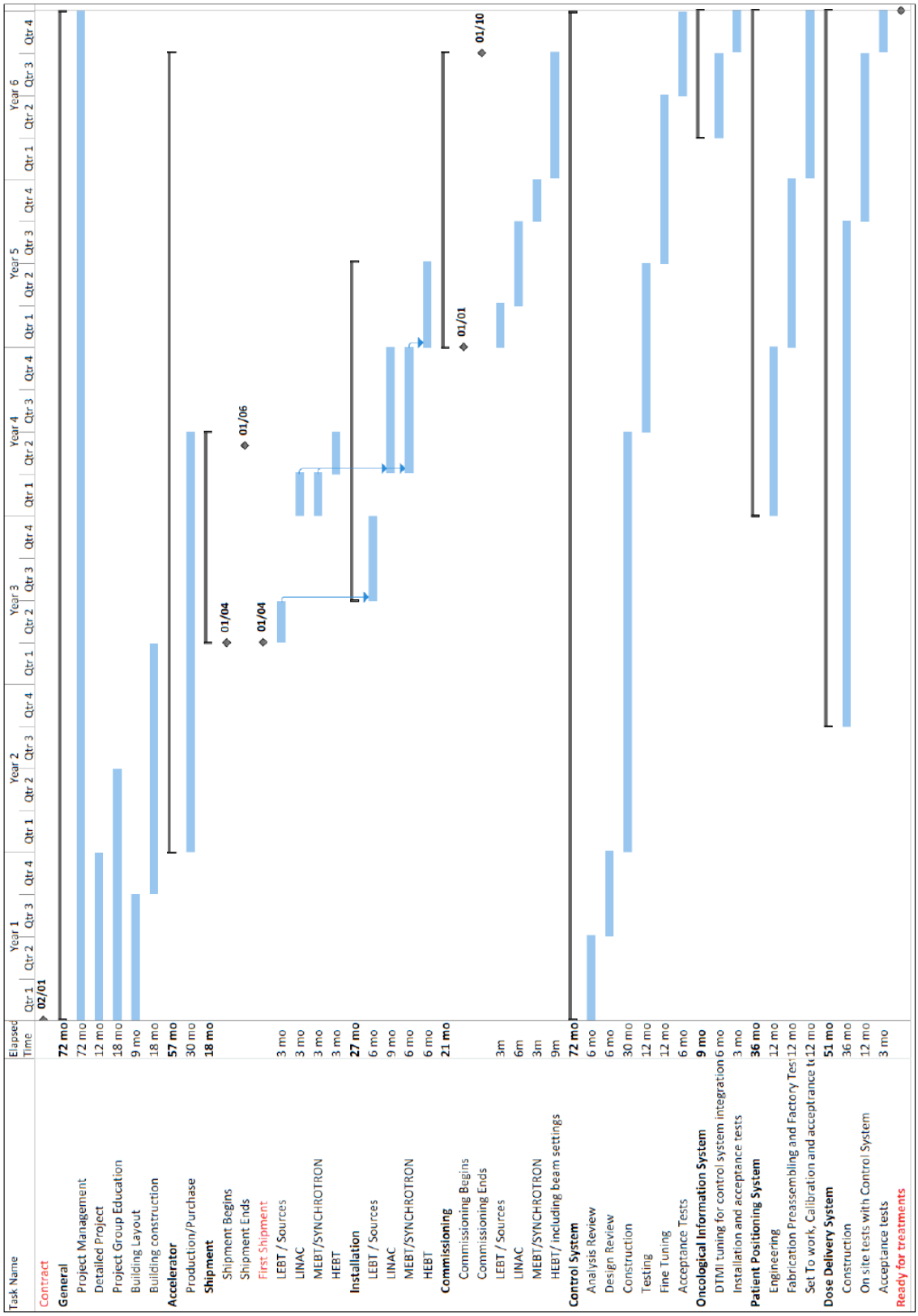

Fig. 31: Time plan for the design, construction, and commissioning of the facility.

At the end of the commissioning phase the local team, always supported by the experts, will constitute the core of the running team that will manage the full complex and use it for both clinical treatment and research activities in radiobiology, animal studies, and medical physics.

2.9 Investments and manpower for the construction and the upgrading

2.9.1 Construction of the Centre

Within the organizational framework described in the last Section, it is possible to estimate the cost of the different subsystem (Table 9). The last column *includes both* the company personnel *and* the personnel of the local team during the 6 years of the construction period.

Table 9: Investments in k€ and man-years for the hardware layout (L/O) (A) of Fig. 30.

L/O	Item	Investments in components (k€)	Man years
Fig. 30A	3 Sources	4,800	4
	Magnets	11,900	93
	Linac	10,700	16
	Power supplies	8,600	68
	Radio Frequency system	600	2
	Beam diagnostics	4,700	39
	Vacuum system	700	14
	Safety system	700	7
	Radiation survey system	300	6
	Horizontal and vertical beamlines for TT2	6,300	5
	Low-energy beamline to EH1	4,700	3
	Total	***54,000***	***257***
	Control and Safety System (CSS)	4,300	99
	Treatment Planning System (TPS)	3,700	2
	Oncological Information Syst. (OIS)	4,100	4
	2 Patient Positioning Systems (for TT1+TT2)	1,400	6
	2 Patient Verification Systems (for TT1+TT2)	3,000	2
	Dosimetry and monitoring devices	600	4
	4 Nozzle assemblies (for TT1+TT2+EH1)	3,000	8
	Equipment for in vitro radiobiology (RB)	300	6
	Equipment for in vivo radiobiology (AT)	800	8
	Equipment for experimental Hall EH1	500	6
	Total	***21,700***	***145***
	TOTAL	**75,700**	**402**

The average European total cost of the about 400 *specialized* man-years, most of them working in high-tech industries, is estimated to be 110 k€/man-year, so that the 402 man-years would need 44 M€ during the six construction years.

Summing 44 M€ to the 76 M€, needed for the material investment, as reported in Table 9 at the end of column 3, a total of 120 M€ is obtained.

The cost of the buildings and shielding of the baseline design has been estimated to be 45,000 k€ so that the total investment is 120,000 + 45,000 = 165,000 k€.

It has to be underlined that this total investment *does not* include

(i) instrumentation for medical diagnostics (CT, PET, CT/PET, MRI…);

(ii) acquisition of intellectual property and legal expenses;

(iii) insurances;

(iv) margin for the constructor;

(v) contingency.

It is worthwhile noting that this sum could be reduced if a sizeable fraction of the personnel working on the Facility construction would be paid with Regional salaries. However, it is too early in the project to be sure that this will happen.

2.9.2 Upgrading of the Centre

The next table concerns the two upgrades: from the layout of Fig. 30A to the one of Fig. 30B and from the layout of Fig. 30B to the one of Fig. 30C.

Table 10: Investments in k€ and man-years for the upgrades of Figs. 30B and 30C.

Layout	**Item**	**Investments in components (k€)**	**Man years**
	2 ion sources (PK isis)	5,200	1
	Upgrade of the HE beamline	500	4
	1 proton gantry	12,000	6
	Total	***17,700***	***11***
Fig. 30B			
	Upgrade of OIS	1,400	4
	Upgrade of TPS	500	-
	Upgrade CSS	150	-
	Total	***2,050***	***4***
TOTAL		**19,750**	**15**
	1 ion source (PK isis)	2,600	1
Fig. 30C	Upgrade of the HE beamline	500	4
	Equipment for experiment hall EH2	1,700	3
(cont. next page))	1 ion gantry	27,000	19
	Total	***31,800***	***28***

Fig. 30C (cont.)	Upgrade of OIS	700	2
	Upgrade of TPS	250	-
	Upgrade CSS	150	-
	1 Nozzle assembly (for EH2)	1,000	1
	Total	***2,100***	***2***
	TOTAL	**34,900**	**30**

The total cost of the two upgrades can be estimated by adding to 19.8 M€ and 34.9 M€ the cost of 15 and 30 man-years respectively. At least half of this personnel will be local and their yearly cost to the Institute will be lower than the average 110,000 k€ /year of the experts of Table 10. Assuming 80,000 k€/year the total costs are 19.8 + 1.2 = 21 M€ and 34.9 + 2.5 = 37.5 M€ respectively.

2.10 Costs of personnel and maintenance during the exploitation

2.10.1 Personnel needed for running the Facility

Table 11 shows that during the operation period (i) 37 people are needed for running the facility, (ii) 33 for the clinical programme and (iii) 8 and 5, respectively, for the radiobiology (in vitro and in vivo) programmes and for the physics programme.

Table 11: Composition of the Running Team during the running phase expressed in 'Full Time Equivalent' experts. AOT and MOT stand for '**A**ccelerator and beams **O**riented **T**echnologies' and '**M**edical and research **O**riented **T**echnologies'.

	Programme	**Speciality**	**Units**
AOT	**M**		
	A	Electronic Engineers	3
	C	Software Engineers	4
	H	Machine Physicists	9
	I	Technicians running the facility	20
	N	Site Manager	1
	E	***Total for AOT***	***37***
MOT	**C**	Senior radiation oncologists	5
	L	Junior radiation oncologists	2
	I	Senior medical physicists	2
	N	Junior medical physicists	4
	I	Nuclear medicine doctors	1
	C.	Anaesthesiologists	1
	P	Medical radiologists	2
		Radiation technicians	12
		Secretaries and nurses	4
	R.	***Total for the clinical programme***	***33***

MOT	**BIOL.**	Senior bioengineers	1
		Junior bioengineers	2
		Radiobiology technicians (also for the animal facility)	5
		Total for the radiobiology programme	***8***
	PHYS.	Senior physicists to support medical physics experiments	1
		Junior physicists	2
		Technician	2
		Total for the medical physics programme	***5***
		TOTAL	**83**

Globally 83 people will form the running team.

2.10.2 Personnel and investments for the exploitation years

As shown in the table, at the end of the commissioning phase about 37 persons will form the machine running team, which will take care of the AOTs by running the centre and upgrading it. The personnel are scaled to run the accelerator H 24, 7/7. Four short maintenance periods are foreseen, one per quarter, during which the technical staff will be in charge of performing and coordinating the systems' maintenance.

The team taking care of MOTs (including the animal facility) will be formed by additional 33+8+5 = 46 persons, mainly radiation oncologists, bioengineers, medical physicists, technicians, and nurses. These numbers appear in the first two rows of Table 12.

Table 12: Personnel and operation costs per year.

Item	**Yearly investment**
Personnel for Accelerator and beams Oriented Technologies (AOTs)	37 persons
Personnel for Medical and research Oriented Technologies (MOTs) [a]	46 persons
Maintenance of hardware and software, spares	5.7 M€
Power at 100 €/MWh	1.2 M€
Personnel (83 persons)	4.0 M€
Total	**10.9 M€**
Income due to the treatment of 250 patients/year	- 5.0 M€
Net sum	**5.9 M€**

[a] It includes radiation oncologists, anaesthesiologists, bioengineers, medical physicists etc.

With an average European cost per expert of 70 k€/year the total cost of 83 full time equivalent persons would be 6.0 M€/ year. Since at least 2/3 of the staff running the Facility will be recruited in the Region, one can estimate that the actual cost will be reduced by 30%, so that the investment in the personnel will be about 4.0 M€/year. This is the figure appearing in Table 12, where it is seen that the total operation cost sums up to about 11 M€/year.

About 50% of the personnel are devoted to MOTs and this produces a non-negligible income since, as said above, the two treatment rooms of the baseline layout will treat (after a ramping up period of about 3 years) 250 patients/year. Assuming an average fee of 20 k€ per full course (which is somewhat low with respect to European standards) after about 3 years of running-in, the income will be about 5 M€/year so that, as indicated in the last row of the table, the net yearly operation cost will be about 6 M€/year.

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Appendix A: World carbon centres and their constructors

Ten centres provide carbon ions: 5 in Japan, 3 in Europe, and 2 in China.

It should be remarked that five of these running centres, Heidelberg, Hyogo, Marburg, Pavia, and Shanghai have 'dual ion accelerators' accelerating both protons and carbon ions; in some cases other ions are also accelerated.

Table A.1 summarizes the main characteristics of the existing carbon ion facilities. The data have been obtained from official publications and the websites of the centres involved.

In spite of the fact that Bob Wilson in his 1946 seminal paper mentioned not only protons and helium but also carbon ions [A.1], carbon ion therapy was initiated fifty years later when, as already mentioned, in 1994 the National Institute of Radiological Sciences (NIRS, Chiba, Japan) treated the first patients using a large synchrotron system named *Heavy Ion Medical Machine Accelerator* (HIMAC, shown in Fig. A.1).

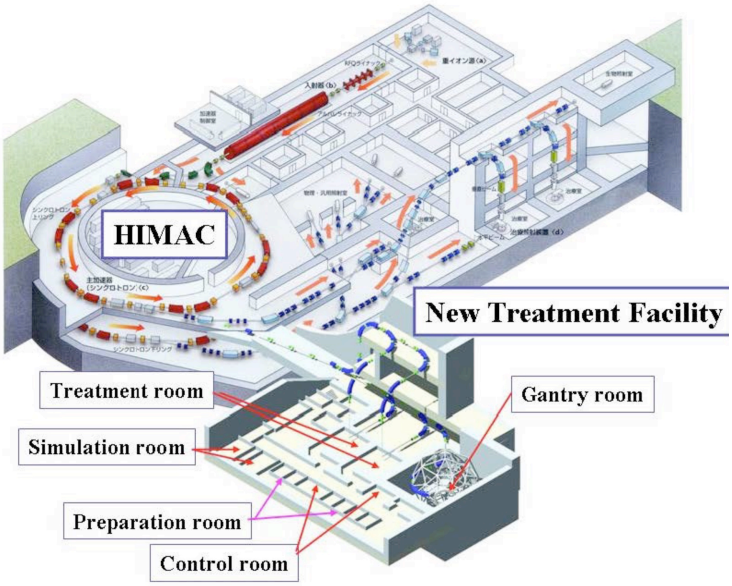

Fig. A.1: The HIMAC accelerator at NIRS, Chiba

In 2010, the centre, which was still in operation with a record of more than 11,000 treated patients, has been enlarged with the addition of three additional treatment rooms with active scanning and a superconducting gantry.

NIRS has acted as the prototype and the technology incubator for the other four centres in Japan that came later and is still at the forefront of technology and research in hadron therapy. Japanese industries—such as Mitsubishi, Toshiba, Sumitomo and Hitachi—were involved in the realization of NIRS and exploited that occasion to develop hadron therapy products that they are now offering on the international market.

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Table A.1: Characteristics of the light ion centres worldwide.

Year of first patient treatment	1994	2001	2006
	HIMAC Chiba (J)	**HIBMC Hyogo (J)**	**Lanzhou HIRFL+CSR (RC)**
Patients treated (Dec 2017)	11,964 C	5,711 p 2,701 C	213
Particles	p, C, O, Ar, Xe	p, He, C	C
Accelerator type	2 Synchrotrons	Synchrotron	Synchrotron
Ion sources	PIG for low Z ECR for high Z	2 ECR	ECR
Injector	RFQ (800 keV/u) Alvarez LINAC (6 MeV/u)	RFQ (1 MeV/u) Alvarez LINAC (5 MeV/u)	Cyclotron
Particle energy (MeV/u)	C <430	p & He 70−230 C 70−320	430 (1,000 max)
Beam particles per spill (pps)	C 6×10^9	p: 7.3×10^{10} He: 1.8×10^{10} C: 1.2×10^9	6×10^9 (physics)
Repetition rate	0.3	p: 1 Hz He and C: 0.5 Hz	
Spill length (ms)	1,000	400	
Dose Rate (Gy RBE/min/l)	5	5	
Beam range (mm)	30−300	p, He: 40−300 C: 13−200	
Beam delivery technique	Passive scattering Intensity controlled 3D raster scan	Passive, respiration gated	Passive and active
Beam S size (mm FWHM)	4–10		
Treatment rooms	3 H, 1 V, and 1 H&V + 1 gantry	p: 1 H and 2 gantry rooms C: 1 H&V and 1 at 45 degree	1H
Treatment field size (cm^2)	Passive: 30 × 40 Active: 20 × 20	15 × 15	

Year of first patient treatment	2009	2010	2011
	HIT Heidelberg (D)	**GUNMA (J)**	**CNAO Pavia (I)**
Patients treated (Dec 2017)	1,800 p 2,800 C	2,711 C	565 p 1,044 C
Particles	p, He, C, O	C	p, He, C, O
Accelerator type	Synchrotron	Synchrotron	Synchrotron
Ion sources	2 ECR	ECR	2 ECR
Injector	RFQ (400 keV/u) IH-DTL LINAC (7 MeV/u)	RFQ APFIH	RFQ (400 keV/u) IH-DTL LINAC (7 MeV/u)
Particle energy (MeV/u)	p 50–250 C 80–430	C 140−400	p 60−250 C 120–400
Beam particles per spill (pps)	p 4×10^{10} He 1×10^{10} C: 1×10^{9} O: 5×10^{8}	C: 1.2×10^{9}	p: 2×10^{10} C: 4×10^{8}
Repetition rate	0.3	0.5	0.3
Spill length (ms)	1,000	500	250−10,000
Dose Rate (Gy RBE/min/l)	5	5	2
Beam range (mm)	20−300	30−250	30−270
Beam delivery technique	Intensity controlled 3D raster scan	Passive, respiration gated	Intensity controlled 3D raster scan
Beam S size (mm FWHM)	4−10		4−10
Treatment rooms	2 H and 1 gantry room	H, V, H&V	2 H and 1 H&V
Treatment field size (cm^2)	20 × 20	15 × 15	20 × 20

Year of first patient treatment	2013	2014	2015	2015
	SAGA HIMAT(J)	**Shanghai (RC)**	**Kanagawa i-Rock (J)**	**Marburg MIT (D)**
Patients treated (Dec 2017)	2,583 C	347 p 723 C	323	120 p 200 C
Particles	C	p, C	C	p, C
Accelerator type	Synchrotron	Synchrotron	Synchrotron	Synchrotron
Ion sources	ECR	2 ECR	ECR	2 ECR
Injector	RFQ (600 keV/u) IH-DTL (4 MeV/u)		Linac	RFQ (400 keV/u) IH-DTL LINAC (7 MeV/u)
Particle energy (MeV/u)	100−400	C 85−430	140−430	C 85−430
Beam particles per spill (pps)	Passive < 1.3×10^9 Active < 3×10^8	p 2×10^{10} C 1×10^9	1.2×10^9	p 2x 10^{10} C 1×10^9
Repetition rate	0.19 Hz	0.3		0.3
Spill length (ms)	3,200	1,000	< 10,000*	1,000
Dose Rate (Gy RBE/min/l)		5	2 Gy/l/min	5
Beam range (mm)	270	20−300	270	20−300
Beam delivery technique	Passive and active	Intensity controlled 3D raster scan	Wobbling and scanning Multi energy extraction	Intensity controlled 3D raster scan
Beam S size (mm FWHM)	2.4−13.7	4−10	4−8	4−10
Treatment rooms	2 H+V, 1 H+45°	3 H	2 H, 2 H+V	3 H and 1 45°
Treatment field size (cm^2)	Passive 15 × 15 Active 22 × 22	20 × 20	20 × 20	20 × 20

Appendix B: Status of the comparisons with X-ray therapy and ablative procedures

B.1 Proton therapy

The table below lists all current prospective comparative and randomized studies of proton therapy versus something else. (It has to be noted that the problem of very long-term side effects and secondary cancers are not endpoints of the current studies [B.1].

Table B.1: Prospective comparative and randomized studies of proton therapy versus X-rays (photons) and ablative procedures.

Name of the study	NCT Number Type of study (patients)	Dates of enrolment	Centres	Results
Comparison of protons versus X-rays				
Radiation therapy in treating patients with stage I or stage II prostate cancer. Protons versus photons	NCT00002703 Randomized (390)	January 1996 End of follow-up September 2005	Loma Linda University Medical Centre and Massachusetts General Hospital, Boston, USA	No results available
Proton/photon RT - benign meningiomas	NCT02947984 Randomized (44)	March 1999 September 2016	Massachusetts General Hospital, Boston, USA	Has results[a]
Trial of image-guided adaptive conformal photon vs proton therapy, with concurrent chemotherapy, for locally advanced non-small cell lung carcinomas	NCT00915005 Randomized (250)	June 2009 June 2019	Massachusetts General Hospital, Boston, USA	No results available
Study of hypo-fractionated proton radiation for low risk prostate cancer	NCT01230866 Randomized (150)	November 2010 December 2018	Mayo Clinic Cancer Centre, USA	No results available
Proton therapy vs. IMRT for low or intermediate risk prostate cancer	NCT01617161 Randomized (400)	July 2012 December 2018	Northwestern Medicine Chicago Proton Centre, USA	No results available
Stereotactic body radiotherapy (SBRT) versus stereotactic body proton therapy (SBPT) of non-small cell lung carcinoma	NCT01511081 Randomized (21)	August 2012 October 2016	University of Texas MD Anderson Cancer Centre, USA	No results available
Randomized trial of intensity-modulated proton beam therapy (IMPT) versus IMRT (photons) for oropharyngeal cancer of the head and neck	NCT01893307 Randomized (360)	August 2013 August 2023	University of California at San Diego, USA	No results available

Comparing photon therapy to proton therapy to treat patients with lung cancer	NCT01993810 Randomized (560)	February 2014 December 2020	University of Florida Health Science Centre, USA	No results available
Proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung cancer	NCT02731001 Randomized (98)	August 2016 April 2020	Department of Radiotherapy and Radiation Oncology, Dresden, Germany	No results available
Phase ii trial of standard chemotherapy (carboplatin & paclitaxel) + various proton beam therapy (PBT) doses for non-small cell lung carcinoma	NCT03132532 Randomized (120)	July 31, 2017 December 2023	Mayo Clinic in Arizona and Rochester, USA	No results available
Comparison of protons versus non-irradiation ablative procedures				
Comparison between radiofrequency ablation and hypo-fractionated proton irradiation for recurrent/residual hepatocellular carcinoma	NCT01963429 Randomized (144)	October 2013 December 2018	National Cancer Centre, Korea	No results available
Proton radiotherapy versus radiofrequency ablation for patients with medium or large hepatocellular carcinoma	NCT02640924 Randomized (166)	January 2016 December 2018	Chang Gung Memorial Hospital, Taiwan	No results available

Data source: ClinicalStudies.gov; October 2017

[a] [B.2]

From these studies one can expect an objective reduction in rates and grades of complications but without very significant impact on either tumour cure rates or on patients' quality of life except for the highly functional regions of body: head and neck, brain, thorax, spine.

To answer the question of how to progress in this area without resorting to unfeasible studies, radiation oncologists propose to rely on a modelling of the medium and long-term side effects as well as the risk of secondary cancers. Works in this direction have been carried out since the 1980s, but a recent acceleration of these developments has been prompted by societal demand for the most efficient allocation of medical resources.

The possibility of predicting for each patient the effect of available treatments makes it possible to optimize the costs. Thus, the field of Model Based Medicine, in the service of personalizing therapeutic choices and optimizing the usefulness of treatments, is the basis for organizations aiming to develop proton therapy in Europe for years to come, in the framework of ESTRO and EORTC. In this sense the Dutch and French projects are exemplary [B.3, B.4].

B.2 Carbon ions and other light ions

As far as light ions are concerned, the state of comparison with X-rays or protons is not much advanced but the development of the numerous NIRS protocols (Chiba, Japan) has undoubtedly demonstrated that carbon therapy is effective in the treatment of many radioresistant tumours. In Europe, treatment reimbursement has been conditioned by the implementation of prospective studies, some of which are comparative and randomized as shown in the table below. The process is beginning and there is no yet a mature study to reach a conclusion today.

It should be noted that the higher relative biological efficiency (RBE) compared to the X-ray makes it difficult to precisely model and anticipate the effect of these treatments. Therefore, the medical measurement of the effects produced by these treatments really requires making prospective comparisons where the two populations compared and treated differently are as much as possible identical. Only randomization allows this in a human population.

Table B.2: Prospective comparative and randomized studies of proton therapy versus X-rays (photons) and ablative procedures.

Name of the studies	NCT Number Type of study (patients)	Dates of enrolment	Centres	Results
Comparison of carbon ions versus X-ray				
Carbon ion radiotherapy for primary glioblastoma vs proton as a boost. (CLEOPATRA)	NCT01165671 Randomized (150)	July 2010 June 2014	Heidelberg University, Germany	No results available
Carbon ion radiotherapy for recurrent gliomas vs stereotactic rt (CINDERELLA)	NCT01166308 Randomized (436)	August 2010 July 2014	Heidelberg University, Germany	No results available
Randomized comparison of proton and carbon ion radiotherapy with advanced photon radiotherapy in skull base meningiomas: the pinocchio trial. (PINOCCHIO)	NCT01795300 Randomized (80)	March 2013 February 2015	Heidelberg University, Germany	No results available
Randomized carbon ions vs standard radiotherapy for radioresistant tumours (PHRC-ETOILE)	NCT02838602 Randomized (250)	October 2017 November 2023	France HADRON, Lyon and Pavia, France and Italy	No results available
Comparison of carbon ions versus protons				
Trial of proton versus carbon ion radiation therapy in patients with chordoma of the skull base	NCT01182779 Randomized (319)	July 2010 August 2015 End of follow-up August 2023	Heidelberg University, Germany	No results available

Trial of proton versus carbon ion radiation therapy in patients with low and inter-mediate grade chondrosarcoma of the skull base	NCT01182753 Randomized (154)	August 2010 August 2022	Heidelberg University, Germany	No results available
Ion irradiation of sacrococcygeal chordoma. Carbon vs protons. (ISAC)	NCT01811394 Randomized (100)	January 2013 June 2019		
Comparison of hadron therapy versus surgery				
Sacral chordoma: surgery versus definitive radiation therapy in primary localized disease. (SACRO)	NCT02986516 Randomized (100)	March 16, 2017 September 2021	European multicentric, Italian sarcoma group	No results available

Data source: ClinicalStudies.gov; October 2017

Even if there is no doubt that these studies will demonstrate the advantage of light ions compared with low LET irradiations, randomized studies in this field are even more necessary than for protons. The importance and conditions of the difference remain to be studied and established. It is therefore necessary, when the SEE Facility will be opened, to set up and expand collaborative networks to participate and initiate multicentric studies.

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Appendix C: Radiotherapy departments in the SEE countries

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The numbers of units per centre are listed in Table C.1 in following the order:

(i) Electron linacs;
(ii) X ray generators;
(iii) Radioisotopes;
(iv) Brachytherapy systems;
(v) Simulators;
(vi) Computer tomography;
(vii) Treatment planning systems.

Table C.1: Number of units.

Centre	1.	2.	3.	4.	5.	6.	7.
ALBANIA							
Hygeia Hospital, Tirana	2				1		1
Mother Teresa Uni Hospital, X-Knife Unit	1						2
'Mother Teresa' University Hospital, Tirana	1	1					1
Total	**4**	**1**			**1**		**4**
BOSNIA and HERZEGOVINA							
Int. Medical Centre, Banja Luka	3			2	1		5
Sveucilišna Klinicka Bolnica, Mostar	2			2			2
Clinical Centre of Sarajevo University, Sarajevo	1		1	2	1		2
University Clinical Centre, Tuzla	2			1			1
Kantonalna Bolnica, Zenica	1						1
Total	**9**		**1**	**7**	**2**		**11**
BULGARIA							
Regional Cancer Centre Hospital, Blagoevgrad				2			
Complex Oncology Centre, Burgas	2			1		1	2
University Hospital, Panagyurishte	1						
University Hospital, Pleven	2					1	
University Hospital, Plovdiv	2		1	3			1

Complex Oncology Centre, Ruse	1	1	1				
Interregional Cancer Hospital, Shumen	2	1		2			
Acibadem City Clinic, Tokuda Hospital, Sofia	1						
Acibadem City Clinic, Uni General Hospital, Sofia	2			1			
University Hospital 'Queen Giovanna', Sofia	2	1				1	4
University Hospital 'St. Ivan Rilski', Sofia	1					1	
Uni Hosp. for Active Treatment in Oncology, Sofia	3	1	1	2	1	1	3
Interregional Cancer Centre Hospital, Stara Zagora		2	1	2		1	1
Sbaloz Dr M. Markov, Varna	1		1		1	1	
University Hospital 'Saint Marina', Varna	3					1	4
Regional Cancer Centre Hospital, Veliko Tarnovo	1	2		2		1	2
Comprehensive Cancer Centre, Vratsa	1		1			1	2
Total	**25**	**8**	**6**	**15**	**2**	**10**	**19**
CROATIA							
University Hospital, Osijek	1			2		1	1
University Hospital, Rijeka	2				1	1	2
University Hospital, Split	2			2	1	2	1
Gynaecological Cancer Centre, Zagreb	2		1		1		1
University Hospital for Tumours, Zagreb	3			1	1	1	2
Uni Hospital Centre 'Sestre milosrdnice', Zagreb	1			2	1	1	2
University Hospital Centre, Zagreb	3		1			2	8
Total	**14**		**2**	**7**	**5**	**8**	**17**
GREECE							
Democritus University of Greece, Alexandroupolis	1		1	2	1	1	1
401 Army General Hospital, Athens			1				1
6th Oncology Hospital 'George Gennimatas', Athens			1		1		1
Agios Savas Oncological Hospital, Athens	3		2	3	1	1	2
Alexandra Hospital, Athens	0		1	2	1	1	1
Areteion Hospital, University of Athens	1				1	1	1
Athens Children's Hospital 'P. A. Kyriakou', Athens	1					1	1
Athinaion Clinic, Athens	1				1	1	1
Evgenidio Foundation Hospital, Athens	1				1	1	1
General Hospital of 'Attikon', Athens	3					1	2
Hygeia Diagnostic & Therapy Centre, Athens	3		1	4	1	1	6
IASO Centre, Athens	4			2	1	1	3
Iatriko Athinon, Athens	2			2		1	3

Iatropolis Magnitiki Tomographia A.E., Halandri	3				1	2
University Hospital, Heraklion	2		3	2	1	2
University Hospital, Ioannina	2				1	1
Oncology Hospital 'Agioi Anargyroi', Kifissia	1				1	1
University Hospital, Larissa	2			1	2	2
IASO Thessalias, Larissa	1				1	1
General Hospital 'O Agios Andreas', Patras	1			1	1	1
University Hospital, Patras	2			1	1	3
Metaxa Anticancer Hospital, Pireus	2	1		1	1	2
Metropolitan Hospital, Pireus	2		2	1	2	3
General Military Army Hospital, Thessaloniki	1				1	1
Axepa University General Hospital, Thessaloniki	2				1	2
Cancer Hospital 'Theagenio', Thessaloniki	2	1		1	1	2
Interbalcan Hospital, Thessaloniki	2				1	2
Papageorgiou General Hospital, Thessaloniki	2		2		1	3
Total	**47**	**9**	**22**	**17**	**28**	**52**
KOSOVO*						
University Clinical Centre of Kosovo, Pristhina	**2**					
FORMER YUGOSLAV REPUBLIC OF MACEDONIA						
Acibadem Sistina Hospital, Skopje	1				1	1
Uni Clinic of Radiotherapy and Oncology, Skopje	3		2	1	1	5
Total	**4**		**2**	**1**	**2**	**6**
MONTENEGRO						
Clinical Centre of Montenegro, Podgorica	**2**		**2**	**1**	**1**	**5**
SERBIA						
Institute for Oncology and Radiology, Belgrade	5		2	1	2	3
Military Medical Academy, Belgrade	1			1	2	3
National Gamma Centre, Belgrade		1			1	1
Health Centre, Kladovo	1	1	2			1
Clinical Centre, Kragujevac	3		2	1	1	2
Clinical Centre, Nis	3		2		1	1
Institute of Oncology, Sremska Kamenica	4		2	1	1	3

* In this document the designation to Kosovo is without prejudice to positions on status and is in line with UNSC 1244/1999 and the ICJ opinion on the Kosovo Declaration.

Inst of Pulmonary Diseases, Sremska Kamenica						1	1
Total	**17**		**2**	**10**	**4**	**9**	**15**
SLOVENIA							
Institute of Oncology, Ljubljana	9	1		9	1	2	5
University Medical Centre, Maribor	2					1	3
Total	**11**	**1**		**9**	**1**	**3**	**8**
TOTAL FOR ALL COUNTRIES	**133**	**10**	**21**	**74**	**34**	**70**	**137**

Appendix D: Materials science with the low/medium energy beam line

Ion beams in the MeV/u energy range are particularly suitable also for materials science applications. The installation of a dedicated beam line for materials research, nanoscience, solid state physics, mineralogy, geosciences, and many other fields would be highly valuable in order to substantially broaden the potential user community of the proposed facility. In the following subsections, the main research fields are briefly summarized.

D.1 Ion beam analysis

Ion beam analysis (IBA) includes a series of analytical techniques with MeV ions in order to probe the composition, elemental depth profile, local chemistry, and structure of solids. IBA methods are quantitative with an accuracy of a few per cent and highly sensitive with a depth resolution of typically few nanometres to a few tens of nanometres. Depending on the beam energy, the analysed depth ranges from a few tens of nanometres to a few tens of micrometres. Typical examples are PIGE or PIXE (particle induced gamma or X-ray emission) often combined with a microbeam that allows the destruction-free determination of the chemical composition with micrometre resolution. Other methods make use of back-scattered projectiles (Rutherford back scattering, RBS) or recoils from the target material (elastic recoil detection analysis, ERDA) to provide information about material properties. Nuclear reaction analysis (NRA) is a nuclear method that is sensitive to particular isotopes and allows concentration measurements vs. depth.

D.2 Material modification

MeV ions can induce pronounced modification of the structural, physical, and chemical properties of a given material. By implantation of a suitable number of specific ion species, e.g., the electrical, oxidation, or corrosion behaviour can be changed.

Another interesting application is the production of microfilters by irradiating thin foils and subsequent track etching. Depending on the choice of ion species, energies, and etching conditions, the size, length, and shape of the resulting channels can be adjusted. By electrodeposition, the channels in ion-track filters can be filled, thereby allowing producing nanostructures such as nanotips, nanowires, nano-antennas, and many more.

D.3 Radiation hardness studies

Ion beams are also useful for testing the radiation hardness of materials used for nuclear waste storage or of electronic components for application in space. Targeted irradiation with micrometre resolution, using a microbeam, allows identification of the most sensitive structures in microchips and the development of appropriate countermeasures.

