Basic concepts for a

SOUTH-EAST EUROPE INTERNATIONAL INSTITUTE FOR SUSTAINABLE TECHNOLOGIES (SEEIIST)

January 15, 2018

THIS DOCUMENT HAS BEEN PRODUCED UNDER THE AUSPICES OF
THE MINISTRY OF SCIENCE, MONTENEGRO

(*) References to Kosovo in this document shall be understood in the context of the UN Security Council resolution 1244 (1999).

Introduction

S. Damjanovic[a] and H. Schopper[b]

The South East European Region is an integral part of Europe but needs the help of the other European countries to develop its sustainable economy and social cohesion. The creation of an international institute devoted to sustainable technologies would be an essential element in such endeavours. The scientific and technological cooperation, including knowledge transfer and training of the young generation would strengthen innovation, information exchange and the development of human capacity building.

A large-scale scientific research facility permitting excellence and internationally competitive activities is a significant means of addressing such common challenges. Since it could not be realised by a single country it requires Regional cooperation and in this way its primary mission of attaining scientific excellence would be complemented by peaceful collaboration in a Region with considerable political frictions.

An initiative to this end was first presented to the World Academy of Arts and Sciences WAAS in 2016 and the government of Montenegro was the first to officially support such a proposal regardless of where the final location would be. Thanks to the engagement of the Montenegrin Minister of Science, Sanja Damjanovic, a meeting of Ministers of Science or their representatives took place on 25 October 2017 (see Fig. 1 below) where a Declaration of Intent was signed to create an international laboratory in the Region with the double objective, following the spirit of CERN, to promote science and technology and to improve the relations between countries. To demonstrate that all signatory parties are treated on an equal level and have the same rights the meeting took place at the neutral CERN premises and was chaired by H. Schopper, former Director-General of CERN. The eight parties signing the declaration were Albania, Bosnia and Herzegovina, Bulgaria, Kosovo*, the FYR Macedonia, Montenegro, Serbia and Slovenia. Croatia agreed also, but for formal reasons had to delay the signature. Greece participated as an observer (see cover figure, blue dots). In the Declaration it is stated that the institute shall operate with the mission of 'Science for Peace' and that the Parties have a common vision and encourage the cooperation of researchers from the Parties.

Thus this initiative to establish a 'SEE Institute for sustainable technologies' has become a regional project. It was also decided to set up a Steering Committee, which will guide in making future decisions.

The success of a similar initiative following the CERN model has been demonstrated recently by the SESAME Project built in Jordan, which unifies member states of different political systems and religions in the Middle East and has achieved that all of them work peacefully together.

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Two options are being considered for the initiative:

- **4th generation Synchrotron Radiation Light Source for Science and Technology (SRL),**
- **Facility for Tumour Hadron Therapy and Biomedical Research (HTR).**

These two options have been chosen since they promise in an outstanding way to achieve the objectives to promote cooperation in the field of science, technology and industry, as well as the education and training of talented young people and engineers based on the transfer of knowledge and technology from European centres.

Representatives at the signing of the Declaration of Intent. (From left) Prof. Blazenka Divjak, *Minister of Science and Education, Republic of Croatia*, Prof. Vladimir Popovic, *State Secretary, Republic of Serbia*, Dr. Tomaz Boh, *State Secretary, Republic of Slovenia*, Mr. Ervin Demo, *Vice Minister of Education and Sports, Republic of Albania*, Mr. Shyqiri Bytyqi, *Minister of Education, Science and Technology, Kosovo**, Dr. Sanja Damjanovic, Minister of Science, *Montenegro*, Prof. Herwig Schopper, *Former Director General of CERN*, Prof. Renata Deskoska, *Minister of Education and Science, The FYR of Macedonia*, Mr. Andrija Pejovic, *Minister of European Affairs, Montenegro*, Dr. Adil Osmanovic, *Minister of Civil Affairs, Bosnia and Herzegovina*, Prof. Kostadin Kostadinov, *Advisor to the Minister of Education and Science, Republic of Bulgaria*, Prof. Costas Fountas, *Scientist, Hellenic Republic*.

Two groups of international experts have worked out Concept Designs for the two options, respectively. These concept ideas are presented in this document. **In some respects the two options offer similar benefits to the Region,** but at the same time they have also complementary aspects that justifies the presentation of both.

The first objective, which both options have in common, is not only to extend existing research activities 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 up mutual trust as has been successfully demonstrated by the case of CERN and SESAME.

Both options have also in common that training of the young generation is an essential and integral part of the initiative. The realisation of the projects 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. In both cases, specialised users in the important fields that will be served by the facilities do not exist yet 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 projects by selecting promising candidates from the Region and finding host laboratories to accept them. The second component of training would be the organisation of workshops and schools for future users. These should be organised by a Training Programme Committee to be set up under the initiative. Contacts have been already established with IAEA at Vienna and the hope is to get financial contributions for such a training programme as it has thankfully been given for SESAME.

Technology and know-how transfer in general are also vital parts of the initiative. In order to make it efficient it is suggested for both options not to order the basic accelerator complexes as a unit from industry but rather with the help of existing experts and laboratories in Europe to create the appropriate team for the facility in question. This is the usual way in which most scientific laboratories have been created in Europe. Only conventional equipment would be bought from the shelf from industry whereas for new developments prototypes will be ordered and later production contracts will be awarded to industry. This allows a large flexibility to use 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 put on the shoulder of industry. To facilitate the collaboration with industry it is envisaged to establish also a kind of 'training programme for and with industry' with the task to explain to firms not yet in contact with research institutions how to cooperate and how to present proposals for adjudication of contracts.

With the building of these facilities 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 is lacking it will be conceivable to establish joint R&D program for pre-series prototypes thus promoting these industries. These prototypes should be manufactured in the SRL member countries by giving their industry a special education/training from other SRS facilities and from the staff of the SRL. With the production of the prototypes, the home industries should be encouraged 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 program, we believe that the technology knowhow transfer program outlined could help in creating a skilled set of scientists which 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.

Finally it should be mentioned that both projects could 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. Both facilities based on particle accelerators need electric power which would be a non-negligible part of the operating cost. To reduce this one could consider installing solar panels. This cannot be considered for the isolated facility since power is needed also when the sun is not shining and 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. Both facilities would serve a large user community which is spread in the Region and even Europe. To transmit data from the central laboratory to the users, a network established for the facility and its users might become a model for a wider network for the Region, as the World Wide Web created for the users of CERN has attained worldwide importance.

In some respects the two options presented are, however, quite different which justifies their consideration and is part of their complementary attraction for the Region. Some aspects may be mentioned.

The two facilities would serve quite different 'users communities'. **A synchrotron radiation light source (SRL) would be attractive to many scientists in universities and also in industry working in many fields, from physics to biology, nanotechnology, environmental problems and even in medicine**. About 1000 scientists would be associated to the facility designing and constructing perhaps their special beams, even if many similar facilities exist in Europe. As in most fundamental sciences it would take some time before any new discoveries would propagate to the market. Also the creation of new spin-off firms might take some time.

A hadron therapy and research facility (HTR) will produce immediate benefits for the health of society but also long range results for biological and medical science. Every year many hundreds foreign medical doctors and scientists will work at the facility, mainly on radiobiology. On the other hand its target is a rather special community, mainly oncology, biomedicine, radiobiology and medical physics. Hence its range for general capacity building would be more restricted than that of a SRL. However, for the proposed combination of therapy and biomedical research, with about 50% of the daily time devoted to research, it would be the first such facility in Europe.

Also as far as the financing is concerned the two options are rather complementary. The SRL facility would be used almost exclusively for research. Therefore the funds for investments and operation would have to come mainly from research programmes, both from the European Commission and the national partners. The HTR, on the other hand, would be used, for about 50% of the operating time, to treat patients and hence the operation would be partially financed from fees mainly paid by national health programmes.

The investment contributions from the EC would be expected to come from the programmes dedicated to the development of Infrastructures.

Concept designs for the two options SRL and HTR are presented in this report. They are not a replacement for full size proposals that will have to be produced by the teams that will be responsible for their implementation. Hence in this report a number of variants for both projects, SRL and HTR, are mentioned and thus leave room and scope for future choices adapted to the final conditions and needs. The results of this report will be presented and

discussed at a Forum on 25/26 January 2018 at the ICTP at Trieste and it is hoped that they will provide an objective basis for further discussion, the final project proposals and to lead to final positive decisions.

Acknowledgements

The valuable advice by N. Sammut (University of Malta) and H. J. Specht (University of Heidelberg) during the development of the initiative is greatly appreciated.

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PART 1

4th Generation Synchrotron Light Source for Science and Technology (SRL)

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1.1 SYNCHROTRON RADIATION FACILITIES

Synchrotron radiation facilities are high brilliance light sources that offer unique possibilities to investigate nature. They provide outstanding tools for both fundamental and applied research investigations and support technology in a wide-range of areas. Indeed **Synchrotron radiation research has become a major factor in the progress of science and technology in all industrially developed countries**.

A general overview of the electromagnetic spectrum is presented in Figure 1.1. Synchrotron radiation light covers the spectrum from ultraviolet to X-Rays.

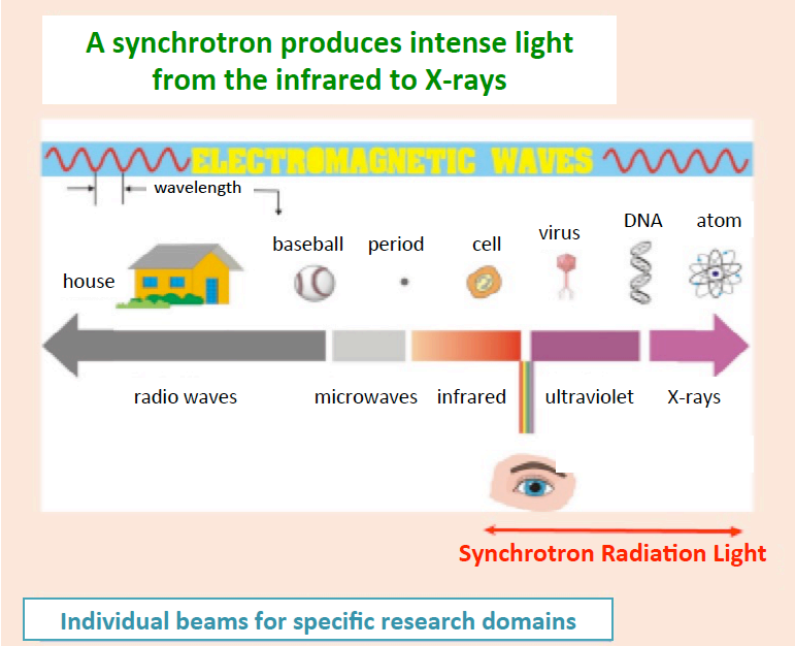

Figure 1.1 *The electromagnetic spectrum from radiation waves to X-Rays.*

More than 60 such light sources exist in the world and 14 in Europe (Figure 1.2).

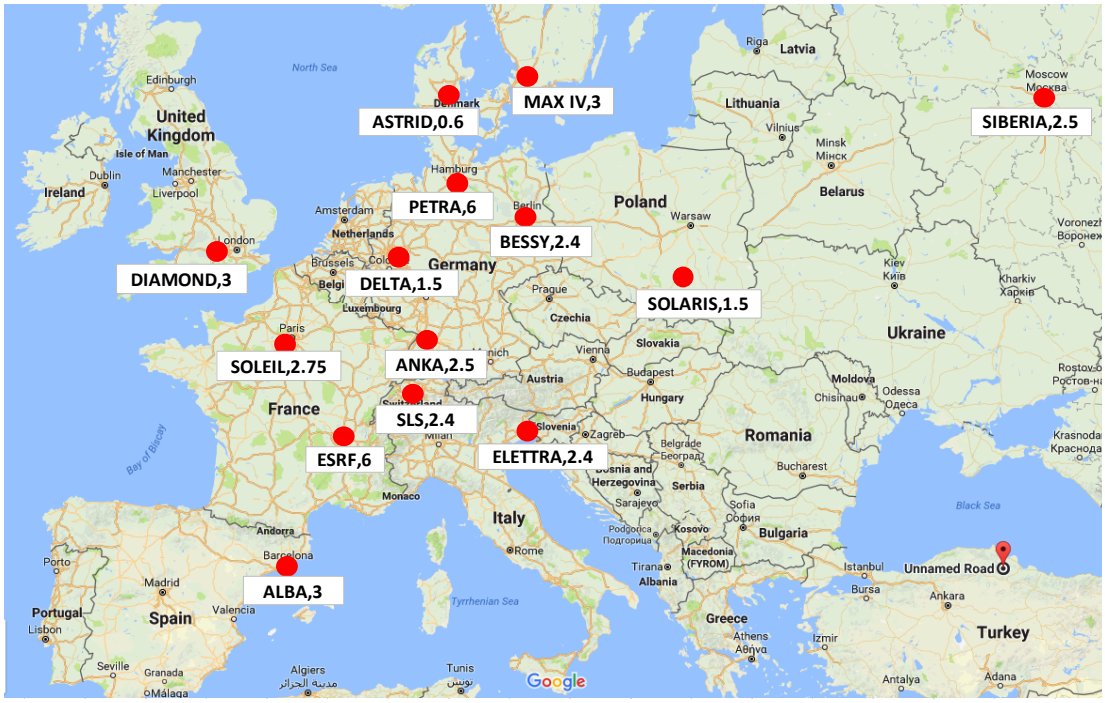

Figure 1.2 *Synchrotron Radiation Light Sources in Europe with the energy expressed in GeV.*

Whilst these 60 facilities share much technology in common, each one is a unique fit to the needs of the users of the facility. **Tens of thousands of users in physics, chemistry, materials science, biomedicine, human heritage, technology and other disciplines exploit these facilities for their research.** Experiments with synchrotron light (Figure 1.3) have produced and continue to produce many landmark results in science and technology. Such a facility offers research capacities for users in almost all universities and research institutes. Increasingly these facilities are becoming an essential part of industrial research and development. In the figure below, just a few examples of research domains, which can be investigated with synchrotron radiation, are shown. The network of users strongly contributes to a culture of equal opportunities for all researchers, overcoming national, financial and gender barriers.

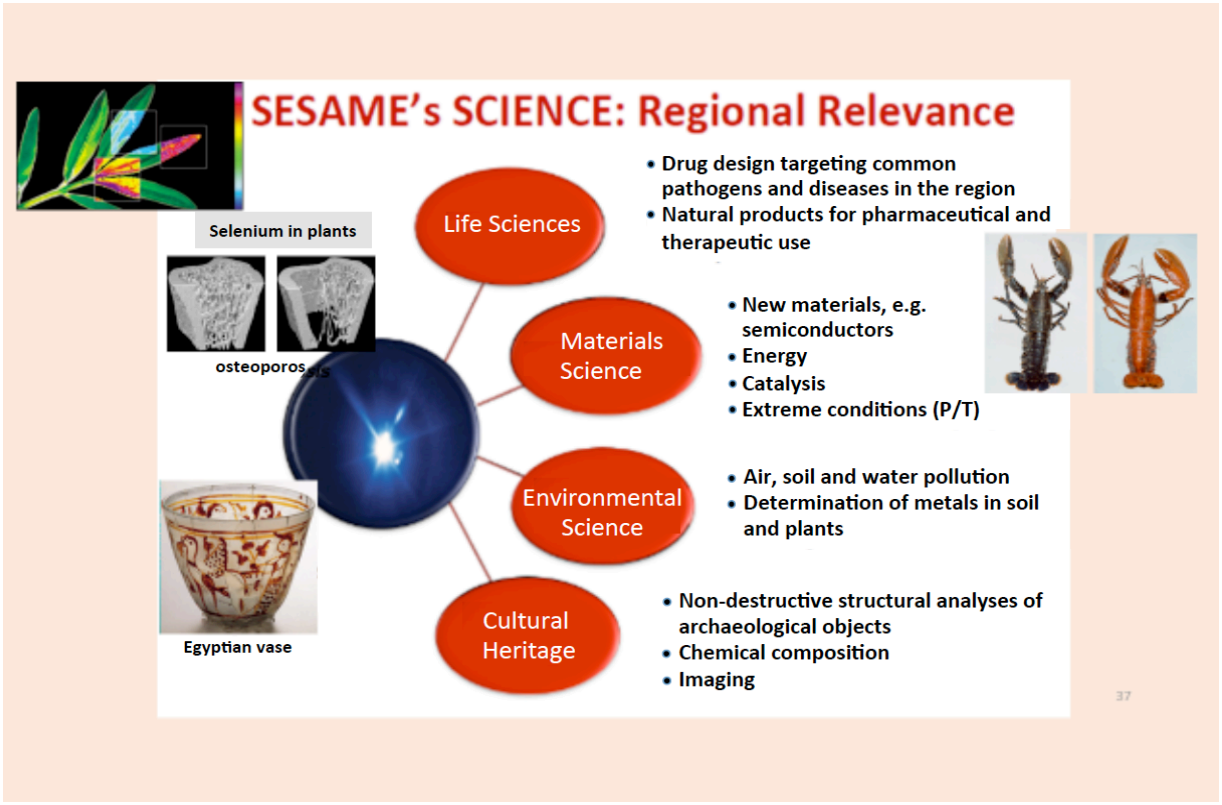

***Figure 1.3**. A selection of domains that can be investigated with synchrotron radiation.*

The facilities themselves have been continuously improved over the years by introducing new technologies and by adapting them to the specific demands of the users. The design of the source and the associated equipment are chosen according to the interests of potential users. Special beam lines can be installed for hard X-rays that are of special interest for structural biology and imaging, whereas infrared beam lines at the other extreme of the spectrum can be used for materials research and archaeology. As a result, none of these many facilities are identical but all are adapted to the needs of a country or a Region.

The users of synchrotron light sources coming from universities, research institutes and also from industry will spend relatively short times at the facility. They will prepare the objects to be investigated at their home institutions, put them into a special beam at the facility, record the data and finally do their analysis at home. The transfer of the data requires and stimulates the creation of a powerful digital network and thereby contributes to the regional digital economy

1.2 WHY A SYNCHROTRON RADIATION FACILITY IN SEE?

The largest part of South-East Europe (SEE) is not so well developed as the countries in the north-, middle- or west of Europe. One factor for the development of a country is how much it supports and invests money in general for education and research. The education system and the research institutes must make it possible to train young people with new ideas for establishing companies and developing new industries. **For a developed country it is mandatory to have research institutions to attract young people and even to reverse the brain drain. Creation of such attractive capacities can better be achieved via an international collaboration and in the spirit of a united Europe, the needed support may be obtained.**

The proposed synchrotron radiation light source (SRL) in the SEE Region would be an outstanding tool to achieve the outlined objectives. A state-of-the-art facility can be built incorporating the most advanced technology used in the best light sources currently in operation. In this way, the facility will be fully competitive on the global scale while minimizing the risks associated to new technologies. New and green technologies can however be included in the design stage, and, even with a more conservative approach, still a wealth of attractive technologies (such as magnets, vacuum system, power supplies, control system, etc.) could be brought into these countries. The construction of the SRL-facility should be performed by young people from the Region, educated at other SRL in Europe by a special training program and led by international experts in this field. They would become specialists in the different areas and could bring new technologies into the countries.

Figure 1.2 shows the distribution of SRLs in Europe and it clearly shows that such facilities do not exist in the SEE countries. The nearest SRL facilities are ELETTRA in Trieste (up to 2.4 GeV) and SOLARIS in Krakow (1.5 GeV). The distance from these facilities to the SEE – countries is in average more than 700 km. The other SRL facilities in Europe are already overbooked and it is very difficult for members of the SEE-countries to get beam time for synchrotron radiation experiments. For some investigations, e.g. in biology, the local proximity of the light source is essential since the specimen to be investigate have limited life times.

It is difficult to overestimate the multi-disciplinary character of such a project, bringing together physics, engineering, biology, and chemistry, enhancing cross cutting-edge research in a vast area of science technology and industrial applications. **In this way the facility will help in creating and sustaining a new generation of young scientists from the Regions involved, for the next 30 years, building research capacity and providing sustainable development for the Region**.

A SRL facility in the SEE Region would be of particular importance for a diversified training program for young scientists and engineers who would become specialist in the different areas and could bring new technological knowhow to the Region. It could also spark several spin-off technologies, which are necessary for the exploitation of the laboratory but could attain a general significance for the Region.

Of course, a close friendly cooperation between the new laboratory and existing light sources will be established because it is the tradition in this field during construction and operation. This will guarantee the most efficient and economical use of these costly facilities. Contacts with the recently founded LEAPs Association (https://www.leaps-

initiative.eu/) have been established. All the institutions support each other to improve the specification of each individual light source. Any new source was supported by existing laboratories in using the most updated technology in the design and even hardware was delivered in many cases. Such mutual help is also provided as far as training is concerned.

1.3 SCIENCE CASE AND SELECTION OF BEAMLINES

The proposal for building a SEE Institute for Sustainable Technology is utterly compelling when the benefit to the peoples of the region is considered. However, the case for building SRL rests ultimately upon the value of the science and technology and the range of areas upon which it impacts. This value will be realised for the SEE region over an extended period of time.

Worldwide, Synchrotron Light Sources provide outstanding and essential insights which touch virtually all aspects of scientific activity, but for every facility a proposal has been made on the basis of the needs of the community which it serves. No single facility can cover every application.

Furthermore, because the first part of the project will build the storage ring and build regional capacity it is envisaged that on Day 1 there should be just three beamlines (applications laboratories). Over a period of time, (perhaps a decade), new beamlines could be built which would allow the facility to grow to full maturity and capacity. A process for choosing beamlines will be established which takes into account the needs of all stakeholders in SEE. Before then, three very general themes can be identified where synchrotron light offers exciting opportunity.

Spectroscopy with X-rays can only be carried out at synchrotron facilities and has applications spanning Physics, Chemistry, Surface Science, Nanoscale Science, Biological science, Environmental and Earth Sciences and interests ranged from the fundamental to industrial applications. Cultural heritage and Conservation Science require access to this tool. This is a chemically selective tool for a large user community and it is a core capacity which is greatly oversubscribed world wide.

Imaging: The first recorded X-ray image was of the hand of Roentgen's wife in 1895 and since that time, imaging has become synonymous with X-rays. In the past two decades there has been a revolution in x-ray imaging which now makes it possible to detect nanometer sized objects in 3D. With Synchrotron light it is possible to image in exquisite detail; examples include - in real time processes of technological importance (welding, processing, corrosion, 3D printing), biomaterials (bone and arterioskeletal disease) and cultural heritage.

Structure: X-rays are the pre-eminent tool for determining the structure of matter at an atomic scale. Synchrotron light allows the structure of large systems (virus, proteins) to be determined in a matter of minutes and it has become an integral part of the pharmaceutical industry and life sciences. Synchrotron light is of equal importance in physics, materials science and materials chemistry where they are playing key role in the development of new battery materials for energy conservation, for green industrial processes and for bioengineering.

The vision is for an Institute which will train and retain the next generation of scientists and technologists within SEE. But it will do much more than this; it will reverse the tide of

migration of talent away from the region in recent years. Most staff in the early years will have been trained outside the region and be returning home. SRL will have unique aspects which, without doubt, will attract scientists from across the world and which will establish the SEE as a zone for excellence.

1.4 DESCRIPTION OF A SYNCHROTRON LIGHT SOURCE

The principal layout of a synchrotron radiation light source (SRL) is presented in Figure 1.4. A SRL consists of two parts: the accelerator complex and the experimental hall with the beam lines.

Synchrotron light is emitted when electrons travelling at close to the speed of light pass through the poles of a magnet. Because it is costly and difficult to make electrons travel this quickly, it makes sense to accelerate them once and then keep them travelling in a circle so that each time they go around the circle (ring) they give out light. This is the primary role of the accelerator complex. This 'circle' of electrons allows many unique, independent and purpose-designed laboratories (beamlines) to be positioned around the ring within a single experimental hall.

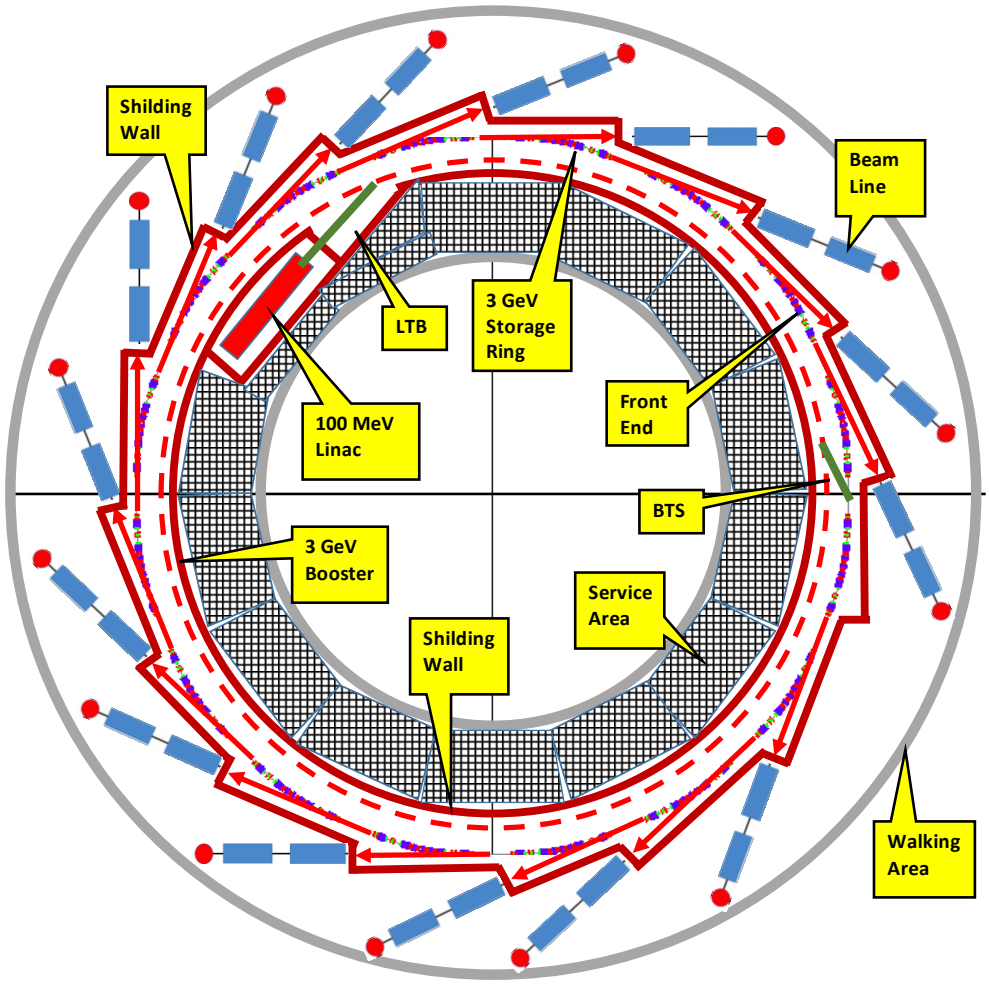

Figure 1.4. *Layout of a Synchrotron Light Source Facility.*

To achieve the necessary high electron energies, they must be accelerated in steps.

First in a linear accelerator up to about 100 MeV, then they are transferred (transfer line LTB) to a booster synchrotron where they can be accelerated to the final storage ring energy and finally they are sent (transfer line BTS) to the storage ring where they are accumulated to provide sufficient light. Since they lose permanently energy by the emission of SR light these losses must be compensated continuously by high frequency accelerating cavities. To keep the electrons together special focussing magnets have to be introduced between the bending magnets. The magnet system together with the high frequency system and an unavoidable vacuum envelope gives a rather complicated technical arrangement with many possibilities to adapt it for cost optimisation. The storage ring consists of a series of so called achromats (up to 30 and more). The technical arrangements of the different components are the same within all achromats. Straight sections with a length of some meters connect the achromats. These straight sections accommodate the insertion devices for producing radiation with a special high brilliance which is tailored for each experimental laboratory (beamline).

Synchrotron light is emitted in these insertion devices and bending magnets. The range of energy of the beams originating at these devices is extremely broad: from ultraviolet up to hard X-rays (Fig.1.9). This is one of the properties which make SR sources so attractive apart from the enormous intensity they provide. From the insertion devices and bending magnets the light is transported by specially designed front ends and beam lines to the experimental hatch in the experimental hall. These beam lines will have very different properties according to the questions to be studied. However, in most cases they will include mirrors and a monochromator, which will select the most appropriate wavelength in the broad spectrum. Some beam lines can be very simple whereas other can be quite demanding technical projects. A layout of a beam line used for the X-ray Absorption Spectroscopy with an overall length of 35m is presented in Figure 1.5.

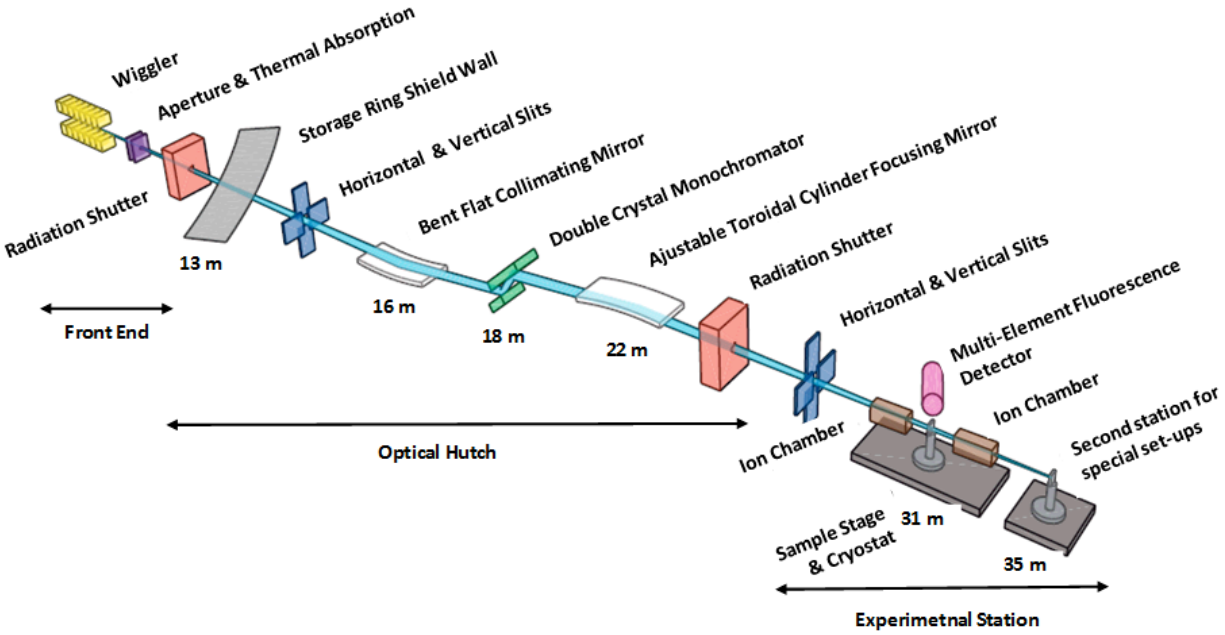

Figure 1.5 *Layout of an X-ray Absorption Spectroscopy Beam Line at the Australian Light Source.*

Synchrotron light facilities are used in many cases as super-microscopes to explore the structures of extremely small objects. In such cases of the resolving power of the radiation is extremely important. This is the smallest distance which can still be resolved. This resolution

power is largely determined by the geometrical properties of the circulating electron beams, the cross section and angular divergence of the beam. The smaller both are, the better the resolution in the experiments will be. To characterise the quality of the machine various parameters are introduced that are, essentially, products of the beam cross-section and the angular divergence; this product is called *emittance* of the beam and is a constant around the ring. These properties depend essentially on the design of the magnets of the machine.

Synchrotron radiation light sources offer another possibility that makes these research instruments so attractive and versatile. If the straight insertions are properly designed special devices can be installed between the bending magnets. These so-called insertion devices are called *wigglers* or *undulators* and can provide light beams with very special characteristics chosen according to the demands of the users. The most recent facilities that were built (e.g. MAX IV at Lund) are designed giving high priority to these beam properties and not so much to higher electron energies. They are called '4th- Generation Light Sources'.

Thus, a synchrotron radiation facility is characterised by a number of parameters which can be chosen by taking into account the interest of potential users, optimisation of construction and operation cost, existing knowhow of future staff and other general aspects. The choice of these parameters is the first major task in preparing a final design.

1.5 DESIGN PARAMETERS OF LIGHT SOURCES

The more than 60 SRL-facilities in the world have energies in the range from 0.5 to 3 GeV. Most users are particularly interested in x-rays and the energy spectrum of the X-rays depends upon the maximum electron energy of the storage ring. Facilities with electrons below 2 GeV will emit mainly soft X-rays with a spectrum up to 10 KeV. Electrons with energies around 3 GeV emit radiation in the hard X-ray regime up to 30 keV.

Many users (mainly those interested in structural molecular research) want to have hard X-ray's and therefore most of the latest SRL are 3 GeV machines to produce hard X-ray's. Because the cost of these facilities rises sharply with energy, one might consider a first stage facility in SEE with an energy of 2.5 GeV. This would save on initial investment, but it would allow for a later upgrade to 3 GeV by adding additional radiofrequency power.

Important for the users is the *brilliance*, which is the numbers of emitted photons normalized to the radiation opening angle and area. The brilliance is inversely proportional to the emittance and proportional to the stored electron current. The emittance is in general proportional to the 3^{rd} power of the deflection angle of the bending magnets. Hence to obtain a small emittance it is much more favourable to install a greater number of short bending magnets instead of long magnets. This is one of the elements of the new concept of MAX IV. Furthermore, the highest brilliances are obtained from insertion devices that are located in the straight sections.

To take advantage of this fact and to enable many beam lines from insertion devices the storage ring should be designed with a sufficient number of straight sections. In addition, it is expected that in the future more users will be looking for a higher degrees of *radiation coherence* in order to open new areas of application of synchrotron radiation. The coherence increases with smaller emittance too. Light Sources that combine all of these

aspects - an emittance smaller as 300 pmrad, a large number of straight sections and a high degree of coherence - are called 4th Generation Light Sources.

In order to be fully competitive, the SEE-Light Source project should be a 4th Generation Light Source. Keeping in mind the mentioned relationships, preliminary studies have shown that the following parameters would offer an attractive compromise between excellent performance and reasonable cost: energy of 2.5 GeV (with possibility to upgrade to 3 GeV), emittances of less than 200 pmrad, circumference not larger than 350 m in order to save investment costs, a magnet lattice with 16 straight section for the installation of insertion devices and a current in the machine of 400 to 500 mA.

Different lattices have been investigated to reach these requirements of a 4th Generation Light Source: 7 Multi-Bend-Achromat (7MBA) as for MAX IV and the upgrade of SLS, Double-Triplet-Achromat (DTBA) as for the upgrade of Diamond and ELETTRA and the Hybrid-Multi-Bend-Achromat (HMBA) as for the ESRF-EBS and the upgrade of APS and other machines. **The result is that a solution based on the HMBA lattice but introducing some new ideas can satisfy the required criteria. For the different components and subsystems, the best-proven technology will be used in order to minimize the cost and risk. This will provide a state-of-the art facility and world leading in some aspects**. The overall capacity for beam lines will be up to 14 insertion devices (10 undulators, 2 wigglers and 2 super conducting wigglers). In addition, several bending magnet beam lines (about 16) can be build up. The choice of the beam lines to be installed at the start of the facility would, of course, depend on the interest of the users.

The proposed design is unique in the sense that it combines the best techniques of previous facilities, e.g. the magnets from the ESRF, the vacuum- and RF-system from MAX IV -Lab, the diagnostic from ALBA (which is reproduced at page 11) etc.

For the injector a 100 MeV Linac as pre-injector and a full energy booster synchrotron will be used. The 100 MeV Linac is a commercial one, the booster synchrotron has to be designed and built for SRL. The booster synchrotron will be located in the machine tunnel in order to save investment cost and to get a small emittance, to reduce the electron losses during injection, to minimize the shielding around the storage ring and to increase the injection efficiency.

1.6 SPECIFIC PARAMETERS FOR THE SOUTH-EAST-EUROPEAN-LIGHT-SOURCE (SRL)

With the parameters chosen in the last section various properties of the design were calculated in order to prove the feasibility of the concept of the proposed South-East-European-Light-Source (SRL).

The arrangement of the magnets in one achromat of the chosen HMBA lattice are presented in Figure 1.6. There are in blue 7 bending magnets, in red 12 quadupoles and in green 8 sextupoles. The layout of 1 quadrant of the proposed SEE-Light-Source, with 4 achromats and 4 straight sections is presented in Figure 1.7. The main parameters are: emittance = 187 pmrad, circumference = 348 m and 16 straight sections (see the table in Figure 1.7). The cross section of the beam in the middle of the straight sections are: σ(horizontal) = 51 μm and σ(vertical) = 4.3 μm.

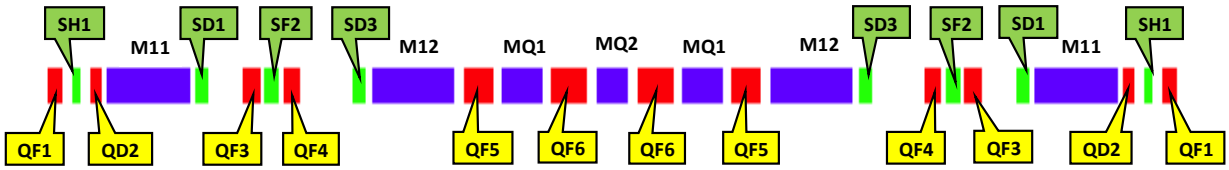

Figure 1.6 *Arrangements of magnets within one achromat.*

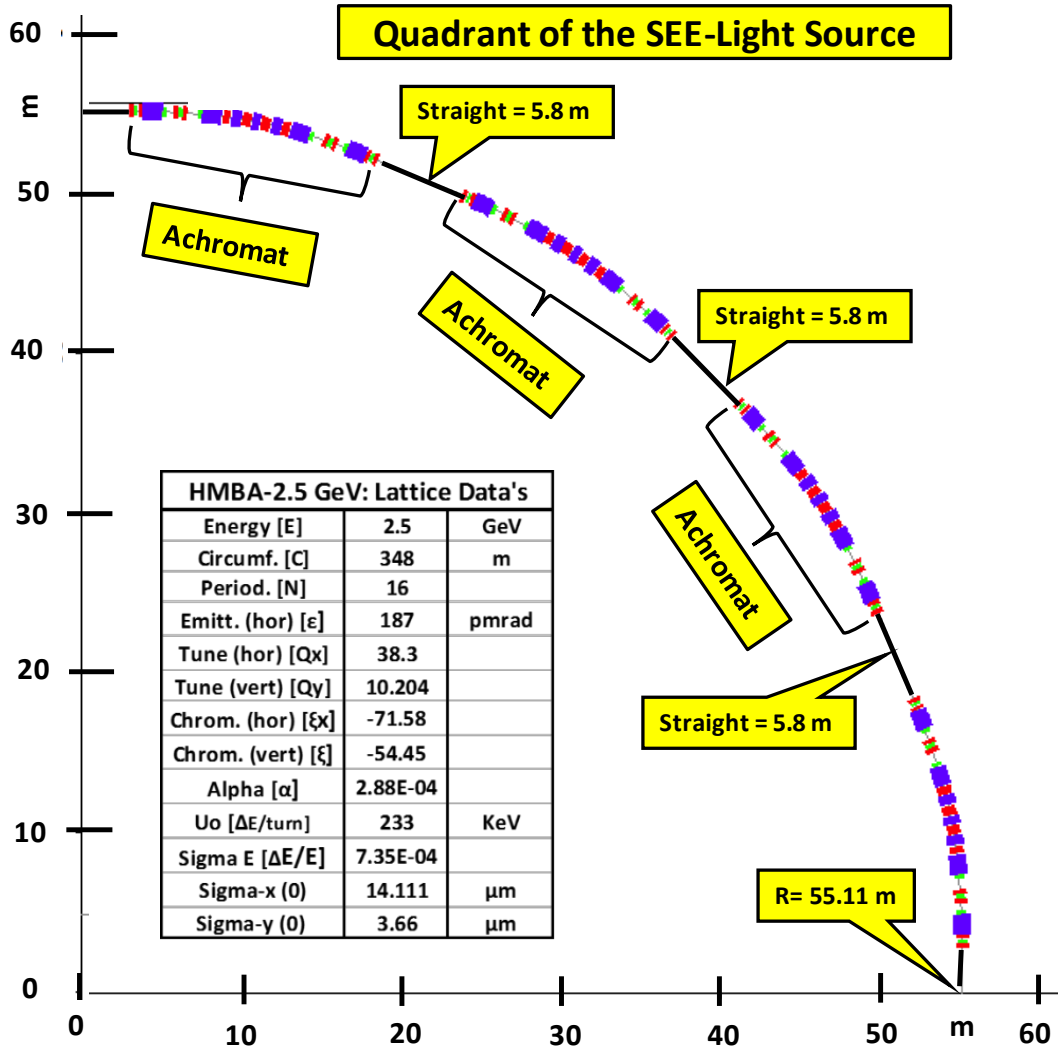

Figure 1.7 *The layout of one quadrant of the storage ring.*

The arrangement of the storage ring and the booster in the machine tunnel is presented in Figure 1.8.

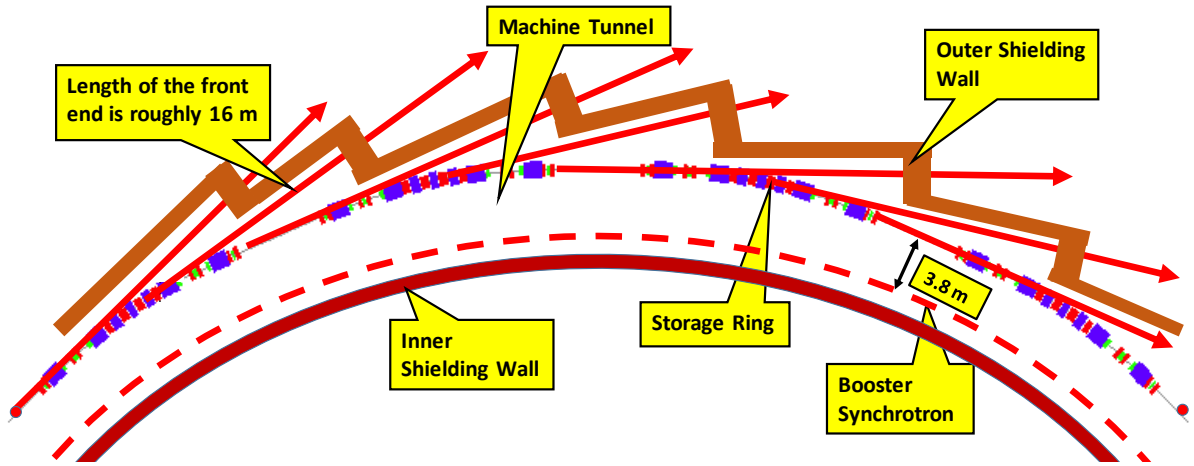

Figure 1.8 *The arrangement of the storage ring and booster synchrotron in the machine tunnel.*

The expected brilliance of the beams emitted from vacuum undulators (UV), superconducting wigglers (SCW), wigglers (Wi) and bending magnets (Bend) from a SRL are presented in Figure 1.9. The radiation spectrum goes up to 70 KeV and brilliances in the 10^{21} Region will be reached.

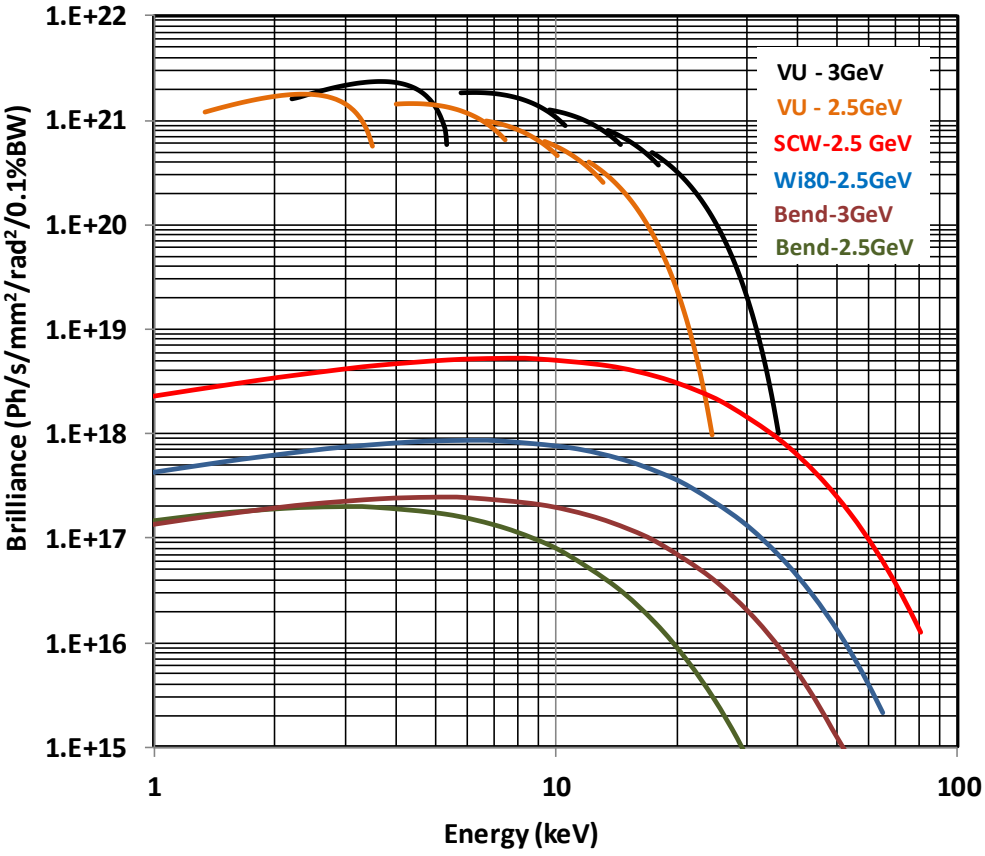

Figure 1.9 *Brilliance of the SRL beams for different sources and energies.*

1.7 RELATION TO EXISTING FACILITIES

No synchrotron radiation facility exists in the Region with an overall population in excess of 30 million with several well-known universities and significant research laboratories. Furthermore, nearby facilities in Europe are overbooked by a factor 2.5 on average per beamline. The facility proposed, even in its initial stages of the phased program will be more than competitive with the existing ones and this will be true for the possible upgrades planned for the next 10 years.

The new laboratory in the SEE-Region will be created in close collaboration with the different light source facilities in Europe in order to get help for training, documentation, etc.

It should be noted that the Accelerator-Community is generally characterized by a strong, supportive collaboration and honest competitiveness between different laboratories in Europe and worldwide. All the institutions support each other to improve the specification of each individual light source and meet regularly in several networks, international conferences and workshops.

If the proposal will be selected for further follow up a formal participation in the newly created LEAPs association will be sought.

1.8 SITE REQUIREMENTS

The site hosting the synchrotron light source should accommodate a circular machine with a circumference of 348 m, and average radius 55.4 m. Adding the space for the front ends of beam lines as well as the shielding wall and the required length of 22 m for the beam lines, the radius of the outer experimental area increases to about 75 m. Including the laboratories and offices the overall diameter of the central building will be roughly 170 m. In addition, the space for the infrastructure as well as storage place and space for parking is needed, **thus the overall size of the site should be about 300 m x 500 m.**

In view of possible future upgrades, considering the lifetime of the facility of 30 years, a possible extension of the site by about 50% would be an advantage.

Another important consideration in the choice of the site is the stability of the ground, which translates in the stability of the stored electron beam in the machine and the beam lines. Nowadays the requirement for stability is in the range of sub–micrometers. **Hence the area of the site should be very stable and no vibrations (by nearby traffic) should disturb the stability of the building and the beam. A good connection to the electric power grid should exist**.

Since the facility will serve a large community of users coming from universities, research laboratories and industry an easy access would be important including easy road access and a not too distant airport. Since most of the users will have to be at the facility for relatively short times a guesthouse would be convenient or at least hotel accommodation should be available in the vicinity.

1.9 TIME SCHEDULE

As far as the design of the machine is concerned a considerable amount of work has been done already which would be made available. Therefore, once the responsible staff has been appointed a detailed proposal could be submitted relatively quickly. The construction could be accelerated if with the help of other laboratories detailed drawings and other documents could be established needed for the tendering process. The estimated time for the design period and the preparation of the call for tender documents is roughly 1.5 years.

The production of the components for the machine and the beam lines takes about 3 years. One year for the prototype or pre-series and 2 years for the series. The building with the infrastructure (electricity, cooling etc.) could advance in parallel and might take perhaps 1 year longer. The building could be built in stages in order to install the 100 MeV pre-injector very soon. This is also true for the 3 GeV booster synchrotron.

About 1 year is needed for the installation of the machines and beam lines. For the commissioning of the machines and the setting up of beam lines about 6 months are required.

In conclusion **about 6 years would be required in total from the approval of the project to the first light in synchrotron radiation experiments**.

1.10 COST ESTIMATES

Investment cost

A firm cost estimate can only be made when the detailed design has been chosen, when the site has been selected and the environmental conditions are known. At this time it is only possible to give some global numbers. The average investment cost for the machine, using the experience from previous projects ALBA, SOLEIL, DIAMOND and MAX IV is roughly 0.25 M€ per meter. With a circumference of 350 m this gives 87.5 M€. Included in this number are the costs for the 100 MeV Linac, 3 GeV booster synchrotron, 2.5 GeV storage ring, transfer lines and front ends.

The necessary investments for the first generation of beam lines can only be estimated when the future users will have expressed their interests. The cost of individual beam lines varies enormously and can range from less than about 1 M€ (infrared beam line) to several millions for sophisticated beams. **Assuming that the facility would start with 3 beams a minimum investment of about 15 M€ may be estimated**. However, at present it is not determined whether the funding of the experiments should be included in the investment of the facility, since at least a part of it could be provided by future users, be it in kind or in money.

It is assumed that the site will be provided free by the host state (this should be taken into account when comparing the total cost estimate made here with the cost of existing facilities since the cost of the land had been a large fraction of the total cost for some projects).

It is very difficult to make an estimation for the cost of the building without knowing its location because the civil engineering cost vary considerably from country to country. Experience from other countries might give an upper limit of about 45 M€.

The overall initial investment for the synchrotron light source could be estimated to be approximately in the range between 150-160 M€ taking into account the mentioned uncertainties. This does not include the cost of the laboratory staff.

For the design, following up the contracts, installation and commissioning roughly 40 people are needed (6 specialist from other SRL (100 k€/year), 15 engineers (50 k€/year) and 20 technicians (30 k€/year). As shown in Table 1.1, overall it makes **11.7** M€ **for the personnel during the construction period of 6 years so that the total investment is estimated to be 160 M€.**

Table 1.1 *Investment cost for initial set up (not including additional laboratories).*

Item	**Investment cost in M€**
Linac, booster, storage ring, front end beams, controls	87.5
First 3 beamlines (average € 5 million/beam)	15. 0
Buildings and shielding	45.0
Laboratory staff during the construction	11.7
Total	**159.2**

The investments needed for the upgrades of the facility are presented in Table 1.2.

Table 1.2*. Investments for possible upgrades (in M€).*

Energy increase from 2.5 to 3 GeV	8
Additional beam lines 10 (average € 5 million/beam)	50
Total	**58**

Personnel

The staff of the laboratory would have to be built-up during the years of construction. At the beginning a few excellent experts will be needed implying internationally competitive salaries. Over time and after training the employment could come from the whole Region. To operate the facility at turn-on about 50 to 60 staff would be required.

Simultaneously with the employment of the staff the operation cost would increase. The staff cost will depend on the salary scales adopted and hence no definite figures can be given at this time. In West European laboratories the average cost for staff per man-year is about 0.061 M€. Assuming that about 2/3 of the personnel would be remunerated according to local salaries one might assume an average cost per year of 0.037 M€/year. **At the start of the facility the cost of the laboratory staff would be about 3 M€/year.**

Operation budget

The operating budget of the facility has two components, one part which depends on the number of operating hours and a second part which is constant.

The experience of most scientific laboratories shows that about 50% of the total budget is personnel cost and their estimate has been given in the previous section. For a synchrotron light source the material budget is to a large extent dependent on the electricity cost which could be as high as 25 % of the total operating budget. With a consumption of 4.5 MW, an operation time of 6500h/year and 100 €/MWh (Western prices) it results in 3 M€/year.

The local cost of electricity should be considered during the site selection. On the other hand it might encourage the development of a solar power project, not just for this facility but also for the benefit of the whole Region.

Adding cost for maintenance and consumables the total yearly operating budget can be estimated to about 9 M€ which would have to be covered by the collaborating partners.

Table 3. *Yearly operating cost.*

Item		M€
Maintenance and consumables		3
Laboratory staff	60 to 70 staff	3
Energy	3.0 MW (western prices)	2 to 3
	Total	**8 to 9**

1.11 EDUCATION AND TRAINING

The training of scientists, engineers and technicians must be considered as a priority from the beginning of the project and a great effort should be made to involve as many staff from the partners of the project as possible. An international training committee with experts in the accelerator field might be established in order to help organizing efficiently the formation and training.

As different areas of expertise and different skills are needed to design, construct and operate such a facility, the knowledge and connection of the members of this committee with international facilities is one important key for the success of this training. At the beginning, the most urgent need would to form and train the experts who would help to design and construct the accelerator complex composed of a linac, a booster and a storage ring. Although, there is always the risk that some of the trainees sent abroad stay there, the scheme applied in the case of the SESAME project was rather successful. A large number of candidates (~100) from the Region can be invited to participate to a school dedicated to particle accelerators and associated technology (~2 weeks) and a selection of few of them (~20-25) can be made, where a specific long term training is offered individually in one of the European laboratories (~18 months). During their training, the selected candidates can also deepen their knowledge by participating in the well-known accelerator schools like CAS (Cern Accelerator School).

The budget of this training program is not negligible and should be elaborated in the beginning. There is hope that the required funds can be obtained outside of the project itself.

PART 2

Facility for Tumour Hadron Therapy and Biomedical Research (HTR)

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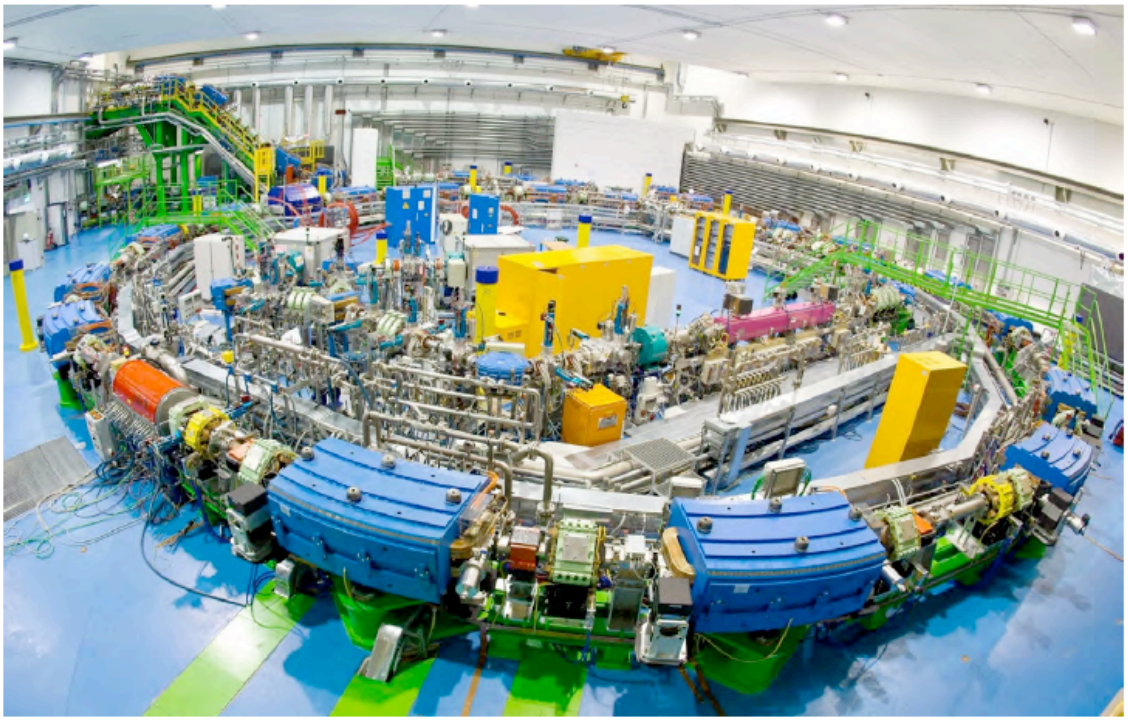

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2.1 THE RATIONALE OF TUMOUR HADRON THERAPY

In Europe about 50% of all tumour patients (i.e. about 2500 patients per 1 million inhabitants every year) are irradiated with X-ray beams produced when electrons, accelerated to about 10 million electronvolts (10 MeV) by a linear accelerator bombard a heavy target. Radiation oncologists aim at depositing in the tumour target large enough energy per unit of mass – a quantity specified by the 'radiation dose'. In biological materials, like cells, X-rays produce single breaks and, more rarely, double breaks of the DNA helix, which however can mostly be repaired by the cell; only one out of about 50 double strand breaks is lethal to the cell, on average.

In the last twenty years a novel radiation therapy has entered in many hospitals: 'hadron therapy' (also called 'particle therapy' or 'ion beam therapy') uses, instead than X-rays, beams of either *protons* or *carbon ions* moving at 30-60 % of the speed of light. (Protons and carbon ions, fully stripped of their electrons, are electrically charged particles made of quarks and belong to a large class of particles called 'hadrons'; this justifies the name 'hadron therapy').

Figure 2.1 explains why hadron therapy is in rapid development so that in 2017 about 70 centres are treating patients worldwide and another 60 are under construction. The left part of the figure shows that X-rays travers the patient body and deposit a decreasing dose *all along their path*; instead beams of protons and carbon ions – bombarding a water target with 140 MeV and 3200 MeV, respectively – lose energy till they stop at a depth of 140 mm. Just before stopping they leave the maximum dose in the so-called 'Bragg peak'.

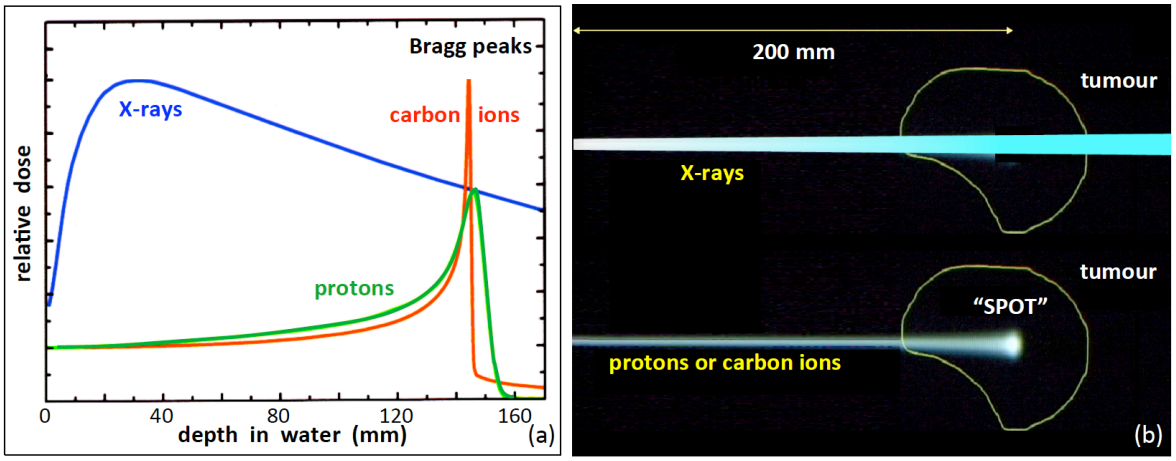

Figure 2.1 (a) *The dose distributions due to beams of X-rays, protons and carbon ions are very different because of the Bragg peaks. (b) In water (and also in soft tissues) the spot is at a depth of 200 mm when the energies of the protons and carbon ions are 170 MeV and 4000 MeV respectively. (In the carbon case a small 'tail', due to nuclear fragments, follows the spot but is not shown.)*

Figure 2.1b shows that **a transversally narrow beam of protons (or ions) produce a *distinct 'spot' of high dose* just before stopping** because (i) in the slowing-down process they are little diffused laterally and (ii) they leave in the Bragg peak the maximal dose. The longitudinal position of the spot is determined by the energy of the particles, which – during a treatment – is adjusted in steps to deposit the dose at different depths, while the transverse positions of the spot are changed to irradiate uniformly the whole tumour target.

Due to the Bragg spot, i**t is possible to concentrate the proton and carbon ion doses on the tumour target, sparing much better than with X-rays normal tissues** located in front 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** as, for instance, the long-term probability of secondary tumours.

The much smaller doses given to healthy tissues is the first advantage of hadron therapy. The example given in Figure 2.2, 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 tissues receive doses that are as large as 50% of the dose given to the tumour. Instead protons coming from only 4 directions irradiate a much smaller volume of healthy tissues. Carbon ions have a similar distribution, with the further advantage that at the border the dose goes to zero on a shorter distance because the spot has a 3-4 mm diameter instead of the about 10 millimetres of a proton spot.

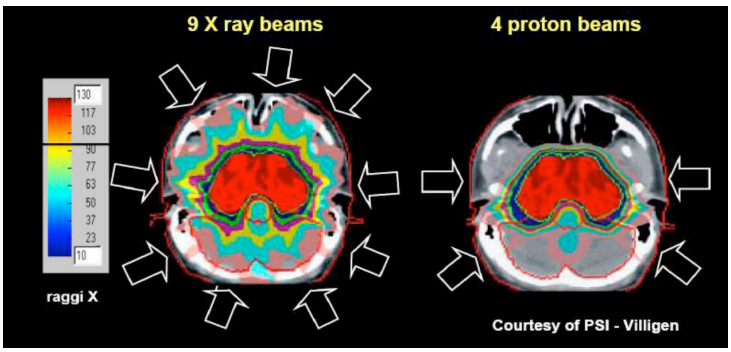

Figure 2.2 *The comparison between two treatment plans of a large skull base tumour shows that normal tissues are much less irradiated when 4 proton beam are used instead than 9 X-ray beams.*

The heart of an electron linear accelerator – called also 'linac' – is small and light: a very special 1-metre long copper tube that has a diameter of about 10 cm. The linac is mounted on a gantry that rotates around the couch where the patient is laying, so that the beam of X-rays – produced when the accelerated electrons hit a heavy target – can be directed towards the solid tumour from any direction. Hadron accelerators are larger, weightier and costlier than X-rays electron linacs because a proton is 2000 times heavier than an electron and has to be accelerated to 250 MeV, instead than 10 MeV, to treat a 30-centimetre deep tumour. Instead than 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.

For treating 30 cm deep solid tumours, **a typical 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 of 6 protons and 6 neutrons and has to be accelerated to 5200 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 during one second for about one million turns.

With a proton beam a uniform dose can be deposited in a tumour target, of any shape and location in the body, by using 2-4 different directions and moving the spot in depth (with the energy) and transversely (with two 'scanning magnets').

It is generally accepted that, for the same dose to the tumour target, the biological and clinical effects of protons are practically identical to the ones of X-rays, even if more *in vivo* studies are needed to clarify the effect of the higher dose density at the end of a proton range in a biological tissue. It is a fact that the knowledge accumulated in more than hundred years of conventional radiotherapy has been directly applied to proton therapy. In particular, to allow the cells of the normal tissue to repair the radiation damage, for both X-rays and protons the dose is subdivided in 25-35 sessions, distributed along 5-7 weeks.

Given the more conformal dose distributions of protons the indications for proton therapy are clear, the treatment protocols are well defined and – by the end of 2017 – about 160,000 patients have been treated with proton beams. Today **many radiation oncologists think protons should be used for those about 10% of the cases in which the tumour is close to 'critical' organs,** so that either a high enough dose cannot be deposited and, thus, the cure rate is not satisfactory or the surrounding dose causes damages to normal tissues and a deterioration of the patient quality. In particular, it is now generally agreed that solid tumours in children should be treated with protons and not with X-rays.

Carbon ions – which are carbon atoms deprived of their six electrons – are a *different type* of radiation: since the electric charge is 6 times larger than the one of a single proton, they produce more severe cell damages than X-rays and protons, in particular in the last centimetres before stopping in the patient's body, where the maximum of the dose is deposited in a 3-4 mm spot. Carbon ions traversing a double helix eject locally many electrons and produce 'clustered damages' that the cell cannot repair; this physics-based *direct* effect concerns about two thirds of the DNA traversals. Instead in an X-rays or proton irradiation in about two thirds of the cases the effects are *indirect* and chemistry-based because free radicals are produced that, reaching the DNA, produce single and double breaks of the helix.

The irreparable clustered damages, produced in the last centimetres of track by **carbon ions, are capable of controlling the so-called 'radioresistant' tumours**, which are about 3-5% of all solid tumours and are poorly controlled by both X-rays and protons. This second advantage of carbon ions with respect to X-rays adds to the first advantage, i.e. the superior conformity of the delivered dose, and is at the root of the specificity and clinical uniqueness of tumour irradiation with carbon ions.

It is worthwhile noting that, since the dose in the normal tissues surroundings the tumour is substantially lower in ion beam therapy, there is no strong reason to subdivide the delivered dose into the 25-35 sessions used for X-rays; for instance, in the NIRS centre in Japan, the pioneer in the field, **carbon ions patients have been treated in 12 sessions and, for some lung tumours, even in a single session**. The overall reduction of the treatment duration is the third advantage of carbon ion treatments; it benefits the patient, who has to come fewer times to the Centre, and increases the overall number of treated patients per year.

The different and larger biological effects produced by ions are measured by their *Relative Biological Effectiveness* (RBE) with respect to X-rays, which can reach values that are as large as 3, meaning that a certain carbon dose produces the same effect as a 3 times larger X-ray dose. RBE determines the outcome of an ion treatment and depends on many parameters. Among them the most important ones are, of course, the type of cell and the type and energy of the hadrons. Other relevant parameters are the number of fractions in which the total dose is subdivided, the oxygenation level of the cells and the presence in the tumour of

substances, which can either potentiate or de-potentiate the effect of the radiation. The phenomena are complex and many of them have still to be investigated.

2.2 GOALS OF THE FACILITY FOR HADRON THERAPY AND BIOMEDICAL RESEARCH

In spite of the 25,000 patients treated with carbon ions, **the RBEs of healthy and tumour human tissues are not well known**. It is not yet generally agreed which tumours are better treated with carbon ions than protons and how many sessions are needed, the irradiation protocols are not yet frozen and it is not clear whether carbon ions are an optimal choice for all types of tumours. For the identification of the tumours to be treated most effectively with carbon ions, the definition of the best protocol for each type of radioresistant tumour – in particular the number of sessions in which the dose has to be fractionated, and the exploration of other radiation fields produced, for instance, by lithium and oxygen ions, **one needs:**

(i) **precise knowledge of the *physical interactions* with biological tissues of carbon ions** and other ions of many different energies;
(ii) ***in vitro* radiobiology experiments** to determine the differential radiobiology and RBEs of carbon and other ions on a large panel of normal and tumour cell lines, with a range of energy levels;
(iii) ***in vivo* determination of the RBE of particles** in different types of normal and cancerous tissues in a range of clinically relevant animal models;
(iv) **comparisons of the outcomes of proton and carbon ion treatments** – in collaboration with other Centres – on the same type of tumours and on many patients.

All these data will also allow the needed accurate modelling, *in silico*, of the many physical and radiobiological phenomena that determine the clinical output of an ion irradiation.

Phase III clinical studies are just beginning in the 11 existing carbon ion centres: 5 in Japan (where in 1994 the first patient was treated with carbon ions), 4 in Europe and 2 in China. But these centres are under pressure to treat patients (in some cases for 10-12 hours per day) and often do not have the sources of other ion species than protons and carbon, so that **worldwide not enough effort is going in research fields listed under the points (ii)-(iv)**.

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

A. **treat with carbon ions and protons, for *about 50% of the day time* and in 2 (4) treatment rooms, 250 (500) patients/year,** to cover a large fraction of the yearly number of Southeast Europe patients having tumours of the highest priority for carbon and proton irradiations;
B. **work, for the *remaining fraction of the day time* – plus nights and weekends, on**
   1. *in vitro* **radiobiology experiments,**
   2. **animal studies** for *in vivo* determination of RBEs and differential radiobiology,
   3. **medical physics measurements**, radiation detectors and optimized treatment planning systems;
C. **contribute** to the invention and implementation of new techniques in the clinical and scientific fields listed under a) and b).

Under point A. 2 and 4 rooms are mentioned because, according to the present plan, the Facility will initially feature 2 treatment rooms which are equivalent to 1 full-time room since the centre will devote about 50% of the day to tumour therapy. According to the

experience of HIT and CNAO, in each full-time room 250 patients can be treated every year, after 3-4 years of ramping-up. With the already foreseen construction of two other rooms as later upgrades of the Facility, the patient flow will increase of 500 patients/year.

Most of these patients will be enrolled in multicentre clinical studies in collaboration with Regional, European and non-European centres.

Because of the ample time devoted to the activities B1, B2 and B3, the animal facility and the many types of sources, the proposed Centre will be unique in the world and will attract medical doctors, biologists and physicists from Europe and other continents.

Collaboration agreements will be signed with many centres of excellence, whose scientists will visit the Facility to perform their experiments. This will give the possibility to the young researchers of the Region to have direct contacts with the leading world experts and to work on frontier research projects, which are by necessity interdisciplinary in the double sense that scientists coming from different specialisations not only will use the *same* accelerator for their work but, more importantly, they will do so having the *same* purpose: improve the treatment of a widely spread and deadly disease.

2.3 CLINICAL AND SCIENTIFIC PROGRAMS

Clinical studies

Cases eligible for hadron therapy are accounting for about 10% of all radiotherapy patients, 1 % of which are in the ***very first level of priority***. As shown in Table 2.1, this corresponds to **about 280 tumours per year (80 for protons and 200 for carbon ions) on a population of ten million people**, so that – as said above - 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.

Table 2.1 *Proton therapy and ion therapy indications of the highest priority.*

Type of tumour eligible with highest priority for proton therapy	**Type of tumour eligible with highest priority for ion therapy (carbon)**
Adult unresectable or relapsing meningioma Other rare adult central nervous system tumours Child central nervous system tumours Any other child solid tumours	Adenoid cystic carcinomas of salivary glands, including head & neck and thorax, sinus adenocarcinomas. Mucinous melanomas of head and neck. Chordomas and chondrosarcomas of skull base and spine. Soft tissues sarcomas of low and medium grade, unresectable or partially unresectable without threatening metastasis. Non small cell lung carcinomas, of small and medium size (N0,M0) unsuitable for surgery. 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**

In Table 2.1 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%.

Beyond the indications of Table 2.1, prospective clinical studies, in collaboration with European and non-European centres, are mandatory to assess group of tumours and to determine the best therapeutic choice for each group, Such results will be critical to convince health authorities to support the offer of ion therapy.

It is easy to understand that such a facility will be a driving force to improve in the Region the medical level in oncology and, may be, beyond oncology, of a whole area of medicine/health care. Actually, epidemiology, data management, trial methodology, public health, health education, medical organizations and networking (for referring patient and clinical studies), medical economics, person servicing, communications, etc. will be enhanced.

***In vitro* radiobiology experiments**

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

When completed the Centre will feature two types of beams to perform this research: the high-energy beam - used also for therapy - which provides carbon ions in the energy range that goes from 1400 MeV to 5000 MeV, and the low-energy beam produced by the injection line at 100 MeV (see Figure 2.4).

There is a range of unresolved radiobiological questions that the Facility will contribute to answer in collaboration with the other European centres, so to

- provide a systematic and coherent dataset of basic radiobiological measurements taken under homogeneous conditions;
- understand the relationship between radiation quality and tumour radio-resistance as well as the impact of partial volume irradiation effects;
- investigate, in the frame of ion therapy, the interaction of drugs, nanoparticles and other biological modifiers of radiation response on the bio-effectiveness of radiotherapy;
- study immune response and immunotherapy with ion therapy.

Animal studies for *in vivo* radiobiology

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 be used for each particular type of tumour. The possibility of devoting ample times to these studies, on various in vivo models, makes the Centre unique in the world landscape.

To fully understand the variation of the RBE and the possible clinical impact thereof, this will be investigated in a systematic, large-scale setup using a panel of clinically relevant *in vivo* models. An in-house animal facility will be established for permanent housing of small rodents. Larger animals will be treated in collaboration with an academic Veterinary Department. Many factors will be studied, such as

- normal tissue tolerance (central nervous system, spinal cord, cartilages, peripheral nerves, optic nerve, etc.),
- dose fractionation,
- different tissue types and position of the irradiated organ along the beam path and the spread-out Bragg peak.

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.

Medical physics

From the 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, the amount of accumulated knowledge is impressive; still many areas are almost uncharted, in particular since the medical community is now moving towards the use of ions different from carbon. Many ion species will be available at the Centre, which will have both the instrumentation and the beam time to study them.

Thus, **to fully expand the therapeutic application of particle beams, there is a range of physics questions to solve**, in close collaboration with the other European and Japanese centres, so to

- 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.
- measure very accurately the stopping power of living tissues by new imaging modalities as for example 'proton-radiography' (tomography).
- develop new beam monitors detecting, 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 also are emitted in these nuclear reactions secondary to fragmentation.
- 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 is currently fully satisfactory; this will be certainly one of the focuses 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.

2.4 THE FACILITY AND ITS EXPERIMENTAL AREAS

The configurations of all the running ions synchrotrons are very similar to the one shown in Figure 2.3. As in the Heidelberg Ion Therapy Centre (HIT) they feature: (1) two (or more) ion sources, (2) an injector linac, (3) a synchrotron, (4) a High Energy Beam Transport line – made of magnets that bend and focus the beam extracted from the synchrotron, (5) horizontal beamlines, which 'paint' the tumour both transversally and longitudinally with a dose spot similar to the one of Figure 2.1, and, sometimes, (6) a carbon ion gantry, which rotates around the patient couch. By the end of 2017 HIT, which was the first European carbon ion and proton centre, has treated with carbon ions 4700 patients.

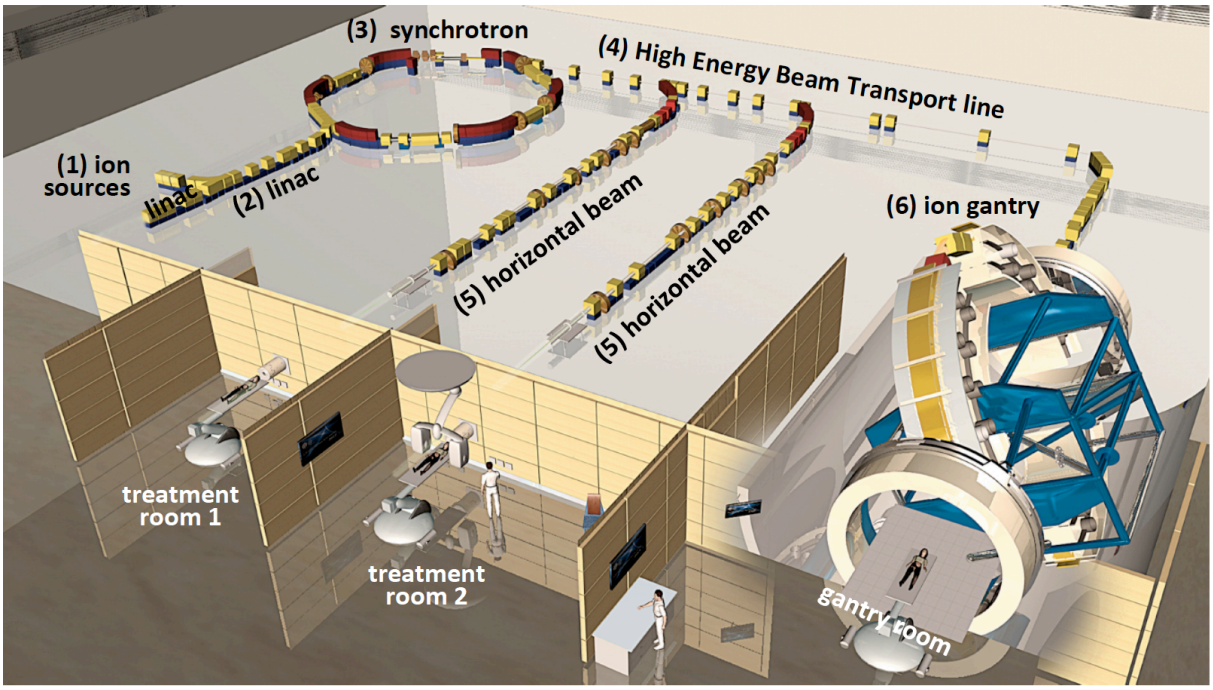

Figure 2.3 *Layout of HIT Centre. The 600 tons gantry was the first in the world to irradiate patients with carbon ions. Since 2015 HIMAC (Japan) irradiates patients with a superconducting gantry.*

This centre was designed by GSI and built with the technical support of Siemens Medical. In GSI, the research Laboratory close to Darmstadt, in the years across the new millennium was held the 'Pilot Project' that treated with carbon ions 440 patients. The centres in Marburg and Shanghai, established by Siemens Company, are further direct descendants of the pilot project.

Two European proton and carbon ion centres have their roots at CERN, which was involved in their design. In fact in 1996 CERN, the TERA Foundation and the MedAustron group project initiated the *Proton and Ion Medical Machine Study* (PIMMS) with the aim of designing a synchrotron and its 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). By the end of 2017 CNAO had treated 1600 patients (75% with carbon ions) and MedAustron had treated about 100 patients (with protons); carbon ion treatment is planned for the middle of 2018.

Since for costing the synchrotron and the transport beam lines it is necessary to choose a specific design, this Report is based on an upgraded version of the PIMMS-CNAO design, which is shown on page 27.

For clinical purpose, the synchrotron accelerates carbon ions – which are made of 12 nucleons – up to 5200 MeV, corresponding to a maximum range in soft tissue equal to 310 mm. Many others ions can be also accelerated to a maximum energy that depends upon the number of nucleons and the electric charge. In particular the maximum ranges of the ions of Helium-4, Oxygen-16 and Argon-36 are >600 mm, 280 mm and 100 mm respectively.

The maximum proton energy from the synchrotron is 1200 MeV; 250 MeV are sufficient for a range in tissue equal to 320 mm but, most probably, also 400 MeV will be used in hadron treatments. The reason is that 400 MeV protons traverse the patient's body with little scattering and, with the technique called 'proton-radiography', can be employed both to calibrate the stopping power of the traversed tissues and to form a beam-view image of the internal organs before initiating the treatment. This information is essential to place the dose spot with a precision of about 1 mm.

It is assumed that, **when completed, the Facility will feature four rooms for tumour treatments** (TT) served by a horizontal beam, a horizontal and a vertical beam, a proton gantry and an ion gantry, respectively, and *two Experimental Halls* (EH). This choice has been made to estimate the investments needed, in money and people, to build and commission the different parts. Of course some of the listed facilities could be different from the present plans and, anyway, the money flow will dictate the final project and its timeline.

2.5 STAGES OF THE PROJECT

The construction of the treatment rooms and the experimental halls can be staged so that a relative small initial investment will allow from the beginning significant clinical and research activities; a possible layout development is shown in Figure 2.4. According to this scenario, the research programs 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. If the staging approach is adopted, at the beginning of the exploitation RB and MP experiments will be performed in the same hall. For radiobiology experiments the Centre will feature also a low-energy beam (7-8 MeV/nucleon), produced by the injector linac.

The construction sequence described in the figure is as follows:

(a) **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) hadrons accelerated by the synchrotron at the highest energies, and a low-energy beam for radiobiology produced by the linac.

(b) **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 could also be mounted in TT1 and TT2. The addition of two high-performance sources is foreseen to widen the research possibilities.

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

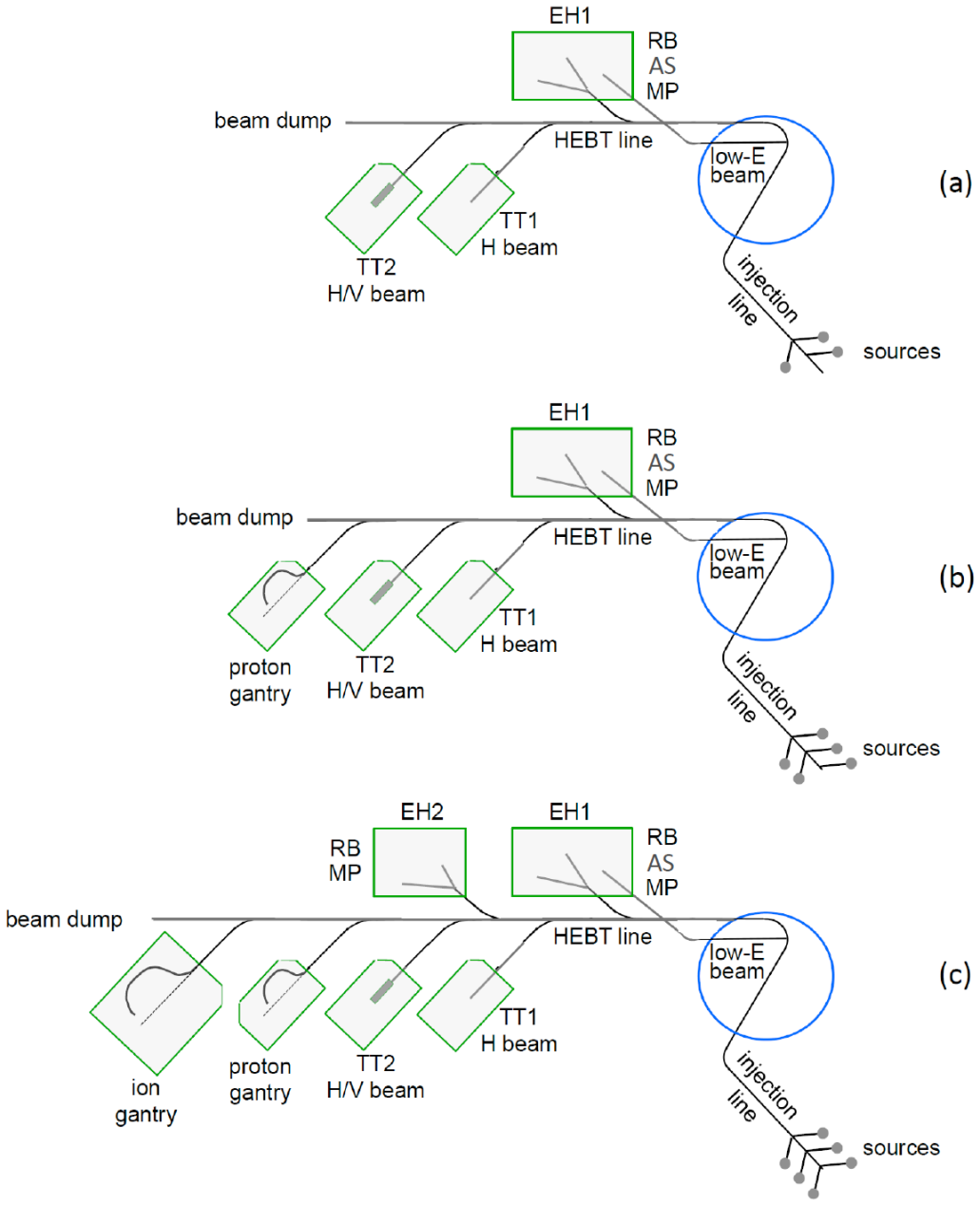

Figure 2.4 *Three possible construction stages.*

The sequence of Figure 2.4 is only one of the many possible scenarios. The one that will be realized will be determined by the goals of the persons in charge at the time together with the time-profile of the inflow of the necessary funds.

2.6 SITE REQUIREMENTS

The layout of Figure 2.4c covers an area of about 150 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 the level of the ground. 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. 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 Figure 2.4c. The electric cabin serving it should have a capacity not smaller than 10 MVA and the water flux for cooling the equipment should be at least 1400 cubic meter per hour.

In the 2-4 rooms of the layouts of figures 2.4a and 2.4c, 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 cares 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 close-by Hospitals.

For program B2 of Sections 2.2, **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 to be 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 could be brought to the site only when needed, and then the follow-up could be done in an external facility. If this solution would be too difficult to realize, an *animal house* will have to be available in the close vicinity of the Centre; its construction could be foreseen as a second phase of the *in vivo* radiobiology program. 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 also where heavy pieces of equipment can be transported and the airport should be not too far, since many scientists will visit the laboratories for performing 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 close-by hotels are needed to host them with their relatives.

2.7 TWO EXTENDED NETWORKS

To reach the clinical and scientific goals ***two Networks*** **will have to be set-up** from the beginning of the project and continuously extended.

The clinical network is the first one. It will allow the local radiation oncologists to work together with their European and non-European colleagues in multicentre prospective comparative clinical studies to improve, simultaneously, the knowledge's in hadron therapy and in classical radiation oncology through the clinical research practice. Secondly, it will give the opportunity of establishing **a *Network of Hospital and Oncological Institutes* of the Region in order to refer patients to the Facility and share clinical prospective investigations and patients' follow-up**. This will need a wide bandwidth connection to exchange medical records and images so that all involved experts will participate in regular teleconferences gathering to discuss patients' cases for medical decision; this is a powerful

tool for professional development and training, data sharing and referral to the Facility of the patients who need a hadron therapy treatment.

The second network is **a *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**. HIT, CNAO and MedAustron will be the main hubs.

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 Program Committee, composed of experts both internal and external to the Facility, will allocate the beam time**.

2.8 TIME SCHEDULE

The time plan foresees *at least* 1 year for the organization of the Management 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.

In total **it would take about 6 years to build and commission the facility.**

2.9 COST ESTIMATES

Investment cost

Table 2.2 lists the estimated investments and the total manpower during the six-year construction-commissioning time. The line 'AOTs' includes all the hardware and the beamlines and the line 'POTs' concerns mainly software as the Control and Safety Systems, the Treatment Planning System, the Oncological Information System, but includes also 4 nozzles (one for TT1 and EH1 and two for TT2), two Patient Positioning System (for TT1 and TT2), equipment for *in vitro* and *in vivo* radiobiology (including the animal facility), dosimeters and monitoring devices.

Table 2.2 *Investments in M€ and man-years for construction and commissioning (in 5 years) of the layout (a) of Figure 2.4.*

Items	Investments in M€	Man-years during construction and commissioning
Accelerator and beams Oriented Technologies (AOTs)	54	258
Patient and radiobiology Oriented Technologies (POTs)	22	142
European cost of the personnel (numbers of the last column)(*)	44	
Buildings and shielding	45	
Total	**165**	**400**

(*) The cost of the personnel (44 M€) is discussed in the next subsection.

Using the information available from the three similar centre built in Europe, it has been evaluated that 45 M€ will be needed for buildings and shielding. Summing the figures of the table, **the investment for constructing and commissioning the layout of Figure 2.4a is 165 M€.** This 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.

The investments needed to add to layout (a) of Figure 2.4 two treatment rooms with a proton gantry and ion gantry – as foreseen in scenarios (b) and (c) – are listed in Table 2.3.

Table 2.3 *Investments in M€ and man-years for possible upgrading by adding to layout (a) of Figure 2.4 the hardware of layouts (b) and (c).*

Item	Investment (M€)	Man years
AOTs and MOTs to go from layout (a) of Figure 2.4 to layout (b)	**20**	15
AOTs and MOTs to go from layout (b) of Figure 2.4 to layout (c)	**35**	30

Personnel

The man-years indicated in the Tables 2.2 and 2.3 take into account the personnel working both in the Construction Team – in charge of the design, follow-up and commissioning of the Centre – and in the companies that produce, mount on-site and commission the many components of the system. The manpower is separated from the hardware because part the personnel will be recruited, as much as possible, in the Region and the cost would be reduced with respect to European cost. In the hypothesis that this is *not the case*, it can be estimated that in Europe the average cost of the needed highly qualified people would be 110 k€/year, so that **the about 400 people involved in the construction and commissioning of the Facility would cost about 44 M€**, as indicated in the fourth row of Table 2.2.

Operation budget

The personnel and the yearly investments needed to run the Facility are listed in Table 2.4.

Table 2.4 *Personnel and operation costs per year.*

Item	Yearly investment
Personnel for Accelerator and beams Oriented Technologies (AOTs)	41 persons
Personnel for Patient and radiobiology Oriented Technologies (POTs) (*)	40 persons
Maintenance of hardware and software, spares	5.7 M€
Power at 100 €/MWh	1.2 M€
Personnel (81 people)	3.5 M€
Total	**10.4 M€**
Income due to the treatment of 250 patients/year	- 5.0 M€
Net Sum	**5.4 M€**

(*) It includes radiation oncologists, anaesthesiologists, bioengineers, medical physicists etc.

As shown in the table, at the end of the commissioning phase **about 40 people will form the Running Team**, which will take care of the AOTs by running the centre and upgrading it. **The team taking care of POTs (including the animal facility) will be formed by other 40 people**, mainly radiation oncologists, medical physicists, bioengineers, technicians and nurses. With European laboratory salaries (61 k€/year) the total cost would be about 5.0 M€/ year. Since at least 2/3 of the staff 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 3.5 M€/year**.** This is the figure appearing in Table 2.4, where it is seen that **the total running cost is approximately 10 M€/year.**

Half of the personnel are devoted to POTs and this produces a non-negligible income since, as said above, the two treatment rooms of the baseline design will treat (after a ramping up period of 3-4 years) 250 patients/year. Assuming an average fee of 20 k€ per full course (which is somewhat low with respect to European standards) the income will be 5 M€/year so that, as indicated in the last row of the table, **the net yearly operation cost will be about 5 M€/year**.

2.10 EDUCATION AND TRAINING

As said at the beginning of Section 2.8, 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 2.7 will be used to train 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.