ISBN: 978-3-95450-214-1 ISSN: 2673-5490 doi:10.18429/JACoW-IPAC2021-MOPAB414

A NOVEL FACILITY FOR CANCER THERAPY AND BIOMEDICAL RESEARCH WITH HEAVY IONS FOR THE SOUTH EAST EUROPEAN INTERNATIONAL INSTITUTE FOR SUSTAINABLE TECHNOLOGIES

S. Damjanovic[1], E. Benedetto[2,3], P. Grübling, M. Sapinski[2,3], H. Schopper
SEEIIST Association, Geneva, Switzerland
M. Durante, P. Foka, C. Graeff, GSI, Darmstadt, Germany
U. Amaldi, TERA Foundation, Novara, Italy
G. Bisoffi[4], M. Dosanjh, M. Vretenar, CERN, Geneva, Switzerland
T. Haberer, HIT, Heidelberg, Germany
S. Rossi, CNAO, Pavia, Italy
H. J. Specht, Universität Heidelberg, Germany
[1]also at GSI, Darmstadt, Germany, [2]also at TERA Foundation, Novara, Italy
[3]also at CERN, Geneva, Switzerland
[4]also at INFN, Legnaro, Italy

Abstract

The South East European International Institute for Sustainable Technologies (SEEIIST) proposes the construction of a major joint Research Infrastructure in the region, to rebuild cooperation after the recent wars and overcome lasting consequences like technology deficits and brain drain, having at its core a facility for cancer therapy and biomedical research with heavy ions.

Beams of ions like Carbon are an advanced way to irradiate tumours, but more research is needed, while the higher investment costs than for other radiation treatments have so far limited the European facilities to only four.

This initiative aims at being strongly innovative, beyond the existing European designs. While the initial baseline relies on a conservative warm-magnet synchrotron, superconducting magnets for an advanced version of the synchrotron and for the gantry are being developed, with a potential for reductions in size, cost, and power consumption. Both warm and superconducting designs feature high beam intensity for faster treatment, and flexible extraction for novel treatment methods. A novel injector linac has the potential for producing radioisotopes in parallel with synchrotron injection.

INTRODUCTION

The accelerator-based Infrastructure for Cancer Therapy and Biomedical Research with heavy ion beams, proposed by the South East European International Institute for Sustainable Technologies (SEEIIST), is an initiative aiming at two crucial strategic goals: enhancing the tools and the knowledge needed in the fight against cancer, and building at the same time international cooperation and scientific capacity in South East Europe [1].

Proposed in principle at a Workshop of the World Academy of Art and Science in Dubrovnik in 2016, with the first official support by the Government of Montenegro in March 2017, the SEEIIST was officially marked as a regional project in October 2017 with a Declaration of Intent for future collaboration signed at CERN between Albania, Bosnia and Herzegovina, Bulgaria, Kosovo, Montenegro, North Macedonia, Serbia and Slovenia; Croatia agreed "ad referendum", while Greece participated as an observer. In January 2018, the International Steering Committee of the SEEIIST was formed, and its members unanimously selected as core of the Institute a facility for cancer research and therapy with heavy ion beams, devoting 50% of its time to biomedical research and 50% to cancer treatment, including clinical trials [2].

SCIENTIFIC AND MEDICAL PROGRAMME

SEEIIST will be mainly a research institution. This is the main difference and advantage compared to the other European ion beam therapy facilities, which focus mainly on treatment of patients and have no or only limited capabilities for research.

The planned scientific programme of SEEIIST is based on four main pillars:

Radiobiology An essential tool to support new therapy solutions such as the novel combined use of particle therapy with immunotherapy, ultra-high dose rate (FLASH) irradiations, mini-beam radiotherapy (MBRT) and space radiation protection, based on the use of multi-ion sources.

Animal studies The majority of the radiobiology studies needs animals, generally rodents. SEEIIST will provide on-site state-of-the-art animal facilities to enable modern radiobiological research. The facility will also offer a unique program in Europe for the treatment of large animals, in collaboration with external Veterinary Departments, with the aim of running comparative trials in pets.

Material science Material research using high-energy ions gives the unique opportunity for testing radiation hardness of space microelectronics and shielding materials, and for investigations of the production of nanotubes.

Medical physics Ultra-fast dose delivery methods will extend ion therapy to moving organs. Together with new

ISBN: 978-3-95450-214-1 ISSN: 2673-5490 doi:10.18429/JACoW-IPAC2021-MOPAB414

synchrotron extraction and delivery systems it will allow FLASH irradiation and ion-acoustic imaging. Moreover, in-beam MRI will generate precious real-time information and pave the way to adaptive treatments.

The medical programme focusses on the treatment of patients with indications for which ion beam therapy is the only or most appropriate therapy option, and on the development of ion therapy with respect to new and advanced treatment protocols, to new indications and to the combination with other treatment modalities. All these treatments will be performed in clinical trials in accordance with international standards.

OVERALL LAYOUT

Figure 1 shows a 3D view of the overall facility, with the position of the clinical section connected to the treatment rooms, the accelerator bunker in the middle (with the roof open to see the accelerator components), and the experimental building to the right.

Figure 1: General 3D view of the SEEIIST facility.

The main principles adopted for the SEEIIST facility are as follows:

- The facility will have three treatment and two experimental beamlines oriented in opposite directions, to physically separate the treatment and the research areas of the facility.
- The three treatment rooms are equipped with a horizontal beamline, a horizontal and vertical beamline, and a rotating gantry, respectively.
- The two experimental beamlines enter a reconfigurable hall, where shielding blocks can be moved to arrange the space and the shielding according to the requirement of the experiments.
- Future extensions are possible, i.e. to add a fourth treatment room equipped with a second gantry and to extend the experimental hall with another beamline.

The overall baseline layout of the SEEIIST facility is presented in Fig. 2. Its main components are:

- three ion sources, providing different beams for experiments and for treatment, with space to add more ion sources if needed for future programmes.
- a linear accelerator (linac) injector.
- a medium energy beam transport (MEBT) line which either transports the ions to the synchrotron injection points or brings them to a dedicated area for beam measurements, which is shielded since in the future it could be used as well for the production of radioisotopes for medical imaging and treatment.
- the synchrotron, which accelerates the beam followed by slow (or fast) extraction at the required energy.
- the high energy beam transport (HEBT) lines, which transfer the beam either to the experimental area or to the treatment rooms.

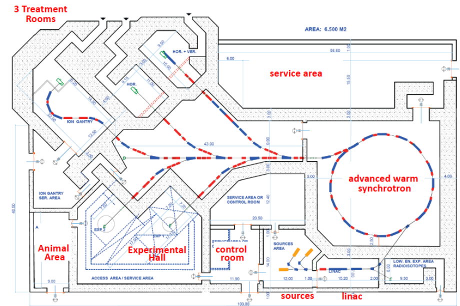

Figure 2: SEEIIST Layout.

TECHNOLOGIES

The initial baseline accelerator layout is based on the PIMMS design [3, 4], conducted at CERN in the period 1996-2000 in collaboration with the TERA and MedAustron groups. The outcome of this study has given birth to CNAO and MedAustron, and has been used as a reference for the initial SEEIIST design described in the "Yellow Report" [2].

Table 1: Baseline Synchrotron Parameters [5]

Ion	**p**	**$^{4}He^{2+}$**	**$^{12}C^{6+}$**	**$^{16}O^{8+}$**
Injection energy (MeV/u)	7			
Rigidity at injection (Tm)	0.38	0.76	0.76	0.76
Energy range at extraction (MeV/u)	60 - 250 (330)	60 - 250	100 - 430	100 - 430
Rigidity at max. energy (Tm)	2.42	4.85	6.62	6.62
Max. field (T)	1.5			
# particles /cycle	2.6e11	8.2e10	2e10	4e10
Ramp-up rate (Tm/s)	<10			
Ramp-down time (s)	<1			
Spill ripple I_{max}/I_{mean} (1 kHz)	<1.5			
Slow extraction spill duration (s)	0.1 - 60			
Fast extraction (s)	$< 0.3\ 10^{-6}$			

While following this baseline layout, the facility adopts a number of advanced state-of-the-art technological solution that will make it a unique world-class facility. In particular it will allow storing and accelerating a record

ISBN: 978-3-95450-214-1 ISSN: 2673-5490 doi:10.18429/JACoW-IPAC2021-MOPAB414

intensity of up to $2{\cdot}10^{10}$ C-ions per cycle - and equivalent intensities for all the other therapy ions, as shown in Table 1, corresponding to a radiation dose of 2 Gy in a 1-liter target. These high stored intensities allow using the most advanced dose delivery techniques.

The main requirements are summarised in Table 1.

Upgraded Injector

All the European carbon ion facilities share with minimum differences the same injector linac design [6]. One of the main directions to be explored for a new linac design consists in increasing the operation frequency, following a trend observed in recent years in the construction of low and medium energy linacs. This allows for higher acceleration efficiency and for smaller dimensions of the accelerating structures, both parameters with a strong impact on the overall cost.

Leading-Edge Multi-Turn Injection and a Multiple Ion Source System

The main challenge for SEEIIST is the increase of the beam intensity, for C-ions up to $2{\cdot}10^{10}$ ions/cycle. This requires the increase of the ion source intensity, a better transmission through the linac and the optimization of the multi-turn injection process. Figure 3 shows the results of the simulations of the multi-turn injection process [7] to have $2{\cdot}10^{10}$ carbon ions accumulated in the accelerator.

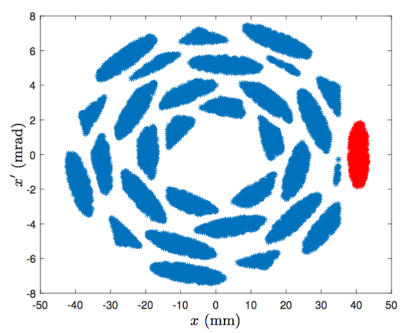

Figure 3: Multi-turn injection simulations from [7].

Multiple Dose Delivery Modalities

Almost all heavy ion facilities in the world either use RF-knockout (RF-KO) extraction or plan to change into this extraction scheme [8]. The RF-KO scheme, in which the beam is excited using the transverse RF signal, allows for easier implementation of multi-energy extraction [9], which has significant benefits to the patients. The SEEIIST synchrotron will use this mode of slow extraction as a default.

Another challenge for Carbon synchrotrons is to obtain the very high dose rates required for FLASH therapy [10]. The maximum can be reached by fast extraction of the beam, and this will be implemented in the SEEIIST machine. The dose delivery to the patient will use a passive scattering method, but the pencil scanning will be available as well in the same irradiation ports.

SEEIIST will also be ready to implement hybrid dose deliver methods. These methods rely on the development of very fast slow extraction techniques, which will be matured in this project.

Novel Superconducting-Magnet Gantry

A novel superconducting gantry design with limited dimensions and weight will allow precise treatments at reduced costs. It is described in [11].

Unique Superconducting Synchrotron Design

In parallel with further optimisation of this baseline concept the SEEIIST accelerator team will engage in the development of more advanced layouts and explore the use of the superconducting magnet technology also for the synchrotron, in the frame of a wide European collaboration. The aim is to reduce the cost and footprint of the facility by introducing technologies that are presently beyond state-of-the-art. The decision on which option to construct will be taken at a later stage of the project, when the alternatives to the present design will be better understood and costed.

The first direction being explored is a revision of the baseline warm-magnets synchrotron lattice, going to new configurations with possibly a lower number of magnets than the PIMMS design. An alternative recently proposed by the University of Melbourne [12] is to use a lattice based on 2 Double-Bend Achromat (DBA) cells, which allows for two dispersion-free straight sections. Their optimised design has 12 dipoles and a circumference of only 55 m.

Recently, the design of a compact SC synchrotron has been developed by the TERA foundation [13], based on 90 degree magnets of Canted Cosine Theta (CCT) type at 3.5 T field, together with the design of a gantry based on the same types of magnet at 4 T. Superconducting CCT magnets are used in many accelerators, including for the LHC luminosity upgrade. For this specific application, the CCT magnets including nested alternating-gradient quadrupoles for combined deflection and focusing (AG-CCT) are based on a development going on at LBNL for proton therapy gantries [14].

CONCLUSIONS

The SEEIIST particle accelerator will provide the largest worldwide quality and variety of beams for cancer therapy and research, thanks to the adoption of beyond state-of-the-art technological solutions discussed in this paper. It will crucially advance research on cancer treatment, offering a multidisciplinary scientific program, which for the first time will be centralized within a single infrastructure. The SEEIIST will close a notable gap in the European RI landscape in what concerns cancer research, one of the five missions of the new Horizon Europe Programme. With its dual task to treat patients and to perform state-of-the-art-research based on innovative solutions, the SEEIIST Project would present a European Center of Excellence for the fight against Cancer, one of the best examples of “Science for Society” projects.

ISBN: 978-3-95450-214-1 ISSN: 2673-5490 doi:10.18429/JACoW-IPAC2021-MOPAB414

REFERENCES

[1] U. Amaldi *et al.*, "South East European International Institute for Sustainable Technologies (SEEIIST)", *Front. Phys.*, vol. 8, Jan. 2021. doi:10.3389/fphy.2020.567466

[2] U. Amaldi *et al.*, "A facility for tumour therapy and biomedical research in South-Eastern Europe", CERN, Geneva, Switzerland, Rep. CERN-2019-002, Jul. 2019.

[3] P. J. Bryan *et al.*, "Proton-Ion Medical Machine Study (PIMMS), vol. 2", Collaboration CERN-TERA Foundation-MedAustron Oncology, Geneva, Switzerland, Rep. CERN-PS-2000-007-DR, 2000.

[4] L. Badano *et al.*, "Proton-Ion Medical Machine Study (PIMMS), vol. 1", Collaboration CERN-TERA Foundation-MedAustron Oncology, Geneva, Switzerland, Rep. CERN-PS-99-010-DI, 2000.

[5] E. Benedetto *et al.*, "Comparison of Accelerator Designs for an Ion Therapy and Research Facility", CERN, Geneva, Switzerland, Rep. CERN-ACC-NOTE-2020-0068; NIMMS-Note-001, Dec, 2020.

[6] A. Bechtold *et al.*, "The RFQ-Drifttube Combination for the Medicine Synchrotron in Heidelberg", in *Proc. LINAC102*, Gyeongju, Korea, Aug. 2002, paper TH480, pp. 1062-1064.

[7] A. Advic, "Multiturn injection of Carbon Ions in a Medical Synchrotron", Master thesis, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, 2020.

[8] S. Savazzi *et al.*, "Implementation of RF-KO Extraction at CNAO", in *Proc. IPAC'19*, Melbourne, Australia, May 2019, pp. 3469-3471. doi:10.18429/JACoW-IPAC2019-THPMP010

[9] K. Mizushima *et al.*, "Experimental studies of systematic multiple-energy operation at HIMAC synchrotron", *Nucl. Instrum. Methods. Phys. Res. Sec. B*, vol. 331, pp. 243–247, Jul. 2014. doi:10.1016/j.nimb.2013.12.033

[10] S. Jolly *et al.*, "Technical challenges for FLASH proton therapy", *Physica Medica,* vol. 78, pp. 71–82, Oct. 2020. doi:10.1016/j.ejmp.2020.08.005

[11] M. Vretenar *et al.*, "The Next Ion Medical Machine Study at CERN: towards a next generation cancer research and therapy facility with ion beams", presented at the 12th Int. Particle Accelerator Conf. (IPAC'21), Campinas, Brazil, May 2021, paper MOPAB413, this conference.

[12] X. Zhang, "Lattice Design of a Carbon-Ion Synchrotron based on Double-Bend Achromat Lens", Jul. 2020. arXiv:2007.11787

[13] E. Benedetto *et al.*, "A Carbon-Ion Superconducting Gantry and a Synchrotron Based on Canted Cosine Theta Magnets", submitted for publication. arXiv:2105.04205

[14] L Brouwer *et al.*, "Design of an Achromatic Superconducting Magnet for a Proton Therapy Gantry", *IEEE Trans. Appl. Supercond.*, vol. 27, pp. 1-6, Jun. 2017. doi:10.1109/tasc.2016.2628305