An Accelerator-based Research Infrastructure for Cancer Therapy and Biomedical Research with Ion Beams

SEEIIST

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South East European International Institute for Sustainable Technologies

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ABOUT SEEIIST

The South East European International Institute for Sustainable Technologies (SEEIIST) is a new International Research Infrastructure to be based in South East Europe, **proposed in 2016 by Prof. H. Schopper, a former Director General of CERN.** The idea of SEEIIST is both, to develop new opportunities for cutting-edge research and technology for the benefit of the region, and to help in the building of mutual trust, as has been successfully demonstrated in the cases of other international research laboratories like CERN in Europe and SESAME in the Middle East. The project received first official political support by the Government of Montenegro, led by **the Minister of Science, Dr. S. Damjanovic in March 2017.** The proposal of adopting as main project for SEEIIST the construction of a pan-European Research Infrastructure for Cancer Therapy and Biomedical Research with ion beams was made around the same time by **Prof. H. J. Specht, a former Scientific Director of GSI** laboratory, one of the pioneers in the use of ion beams to treat cancer, and Dr. N. Sammut, University of Malta. **Prof. U. Amaldi, formerly at CERN** and another pioneer in the design of particle accelerators for cancer treatment joined the effort in 2017 as editor of the first Conceptual Design Report on a possible SEEIIST facility for cancer therapy. The choice of such a Facility as core of its programme was unanimously approved by the SEEIIST Steering Committee in **early 2018**.

The SEEIIST is based on a **Declaration of Intent** signed on **25 October 2017** by Albania, Bosnia & Herzegovina, Bulgaria, Kosovo*, Montenegro, North Macedonia, Serbia and Slovenia at a Ministerial meeting held at CERN. Croatia and Greece took an observer status.

The Declaration of Intent was followed by a stronger **Memorandum of Cooperation** signed on **5 July 2019** by six Prime Ministers of the SEE region (Albania, Bosnia and Herzegovina, Bulgaria, Kosovo*, Montenegro and North Macedonia) at the **Summit of the Berlin Process in Poznan, Poland.**

SEE IIST
South East European International Institute for Sustainable Technologies

* 'This designation is without prejudice to positions on status, and is in line with UNSC 1244 and the ICJ Opinion on the Kosovo Declaration of Independence.'

Western Europe has a growing number of Particle Therapy (PT) facilities.

The **SEE region** with a total population of about 40 million has no facility for PT (grey zone).

CERN - Conseil Européen pour la Recherche Nucléaire
SESAME – Synchrotron-light for Experimental Science and Applications in the Middle East
GSI - Gesellschaft für Schwerionenforschung

MISSION, VISION, GOALS

SEEIIST will offer Multidisciplinary research with a Breakthrough in technologies

SEEIIST will provide State-of-the-art cancer treatment including for the tumours that are difficult-to-treat otherwise

SEEIIST will foster Collaboration through Science Diplomacy

COMBATING CANCER

- SEE region needs a common state-of-the-art infrastructure to promote a Pan-European collaboration and excellent research for the benefit of the citizens.

VISION

- SEE region needs promotion of coherent and collaborative research efforts, which are aligned with the research strategy of the EU.
- The proposed research infrastructure will slow down or even reverse the brain drain of the young talented scientists from the SEE region.

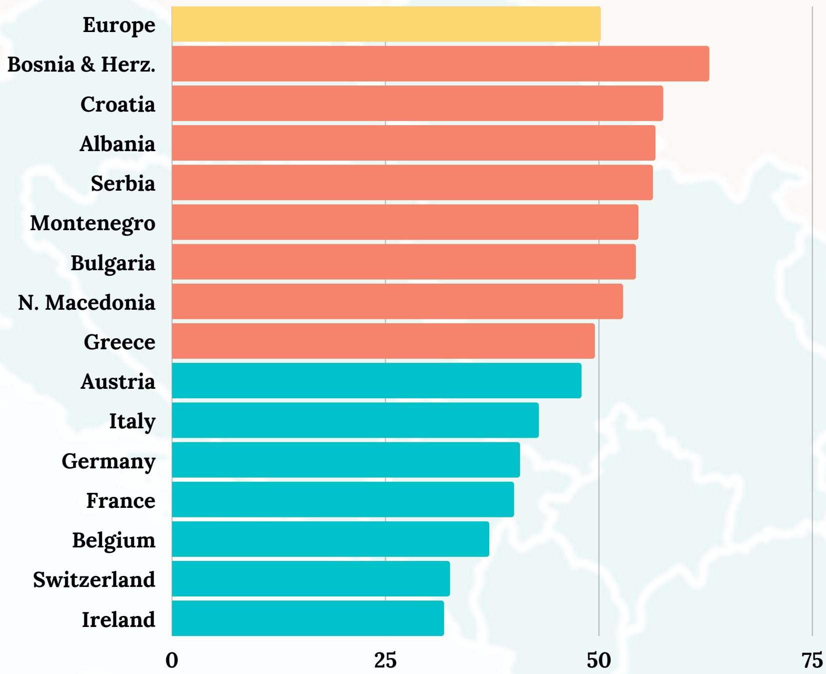
GOALS

- To involve local industry in the SEEIIST construction— over 200 companies would be involved.
- To enable the participating countries to access modern cancer patient treatment.
- **To establish a distributed infrastructure with multiple Hubs in the SEE region** e.g. a Digital Hub for large data storing and handling - Machine Learning and Artificial Intelligence for patient selection, treatment optimisation and follow-up.
- To create a Collaborative platform of clinicians, scientists and users, involving SEE and Western Europe.
- To boost the socio-economic development, attracting the young talented people from SEE and from outside

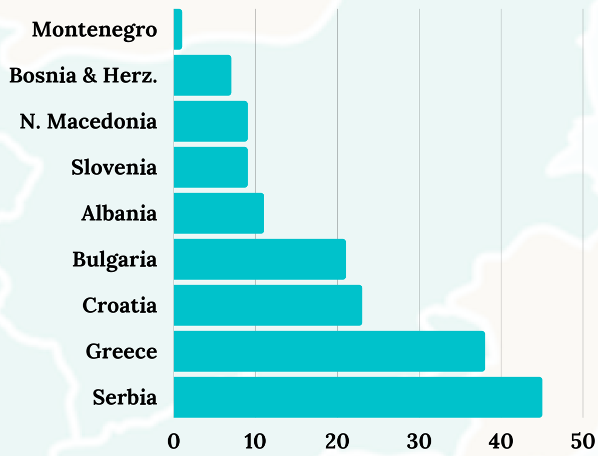
CANCER SCENE IN SOUTH EAST EUROPE

The SEE countries are facing more challenges compared to Western Europe in combating cancer because of the lack of modern early diagnostic tools and state-of-the-art treatment.

Mortality-to-Incidence, All cancers, Both sexes 2018 [%]



Estimated Incidence of cancer in Brain and central nervous system, Both sexes, Ages 0-14 (Total SEE=164)



The mortality-to-incidence ratio (MIR) is calculated for selected cancers and population.
It is an indicator of patient survival and cancer management quality in the respective countries.
The mortality-to-incidence ratio in the SEE countries is much higher compared to the countries of Western Europe, **up to a factor of 2.**

42 M — Total Population of SEE region

1000 — New cancer cases in children for 2018 in SEE, ages 0-14

222 000 — Number of new cancer cases in SEE for 2018 (all ages,both sexes)

120 000 — Mortality rate in SEE for 2018

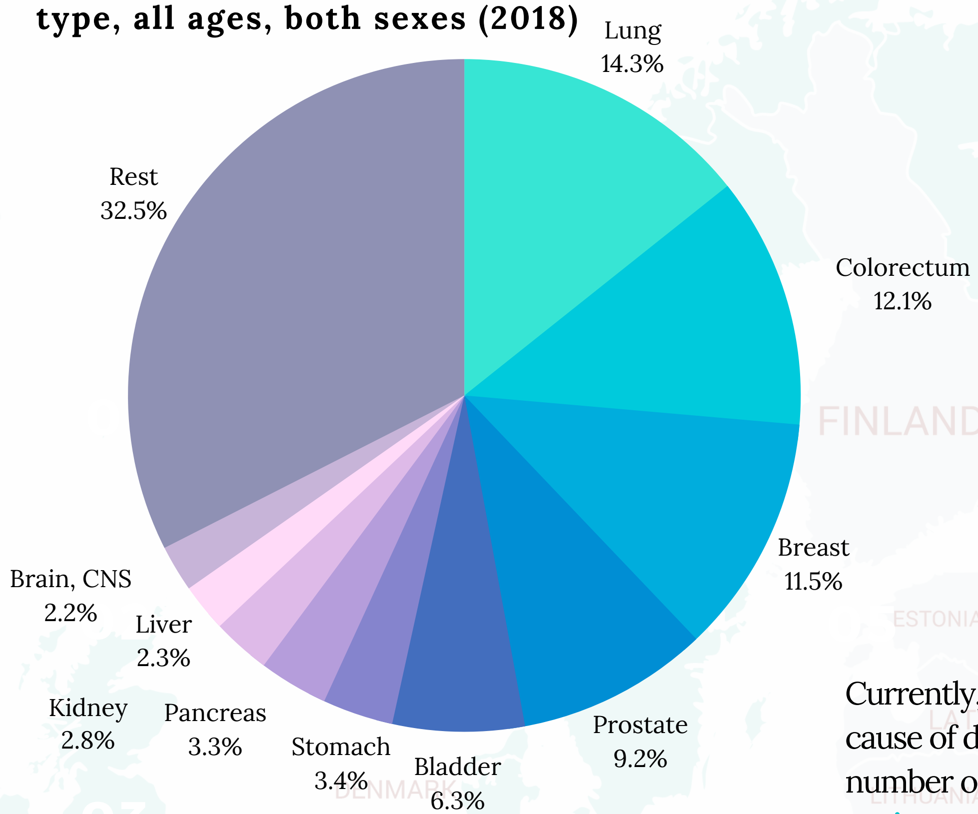
2,3 M — New cancer cases in Europe for 2018 (all ages, both sexes)

243 000 — Projected number of new cancer cases in SEE for 2030

Source: Globocan, 2018

SEE REGION IN NUMBERS

Estimated incidence in SEE region by cancer type, all ages, both sexes (2018)

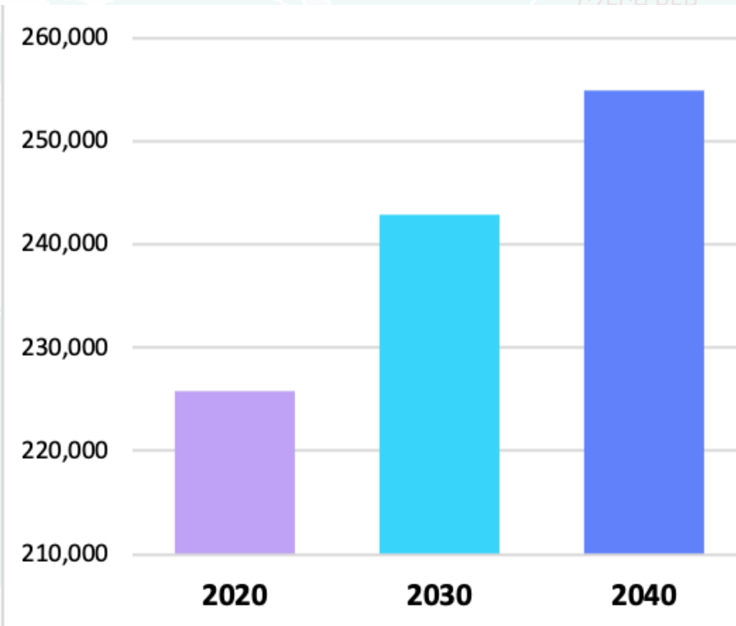


Cancer site	No. of cases in SEE for 2018
Lung	31 783
Colorectum	26 872
Breast	25 571
Prostate	20498
Bladder	14091
Stomach	7 552
Pancreas	7 406
Kidney	6 213
Liver	5 128
Brain and CNS	4 979
Rest	72 222
TOTAL Number	**222 315**

Cancer is a major regional and societal challenge. Worldwide, in 2018 alone, **18.1 million cases were diagnosed,** 9.6 million people died and 43.8 million people were living with cancer.

Currently, cancer is the second leading cause of death, but it is projected to become number one in the coming years. The battle against cancer is a top priority for our society. In particular, there is an urgent need to develop cancer therapies that can cure difficult cases.

Estimated number of new cancer cases in SEE in the future (2020-2040)



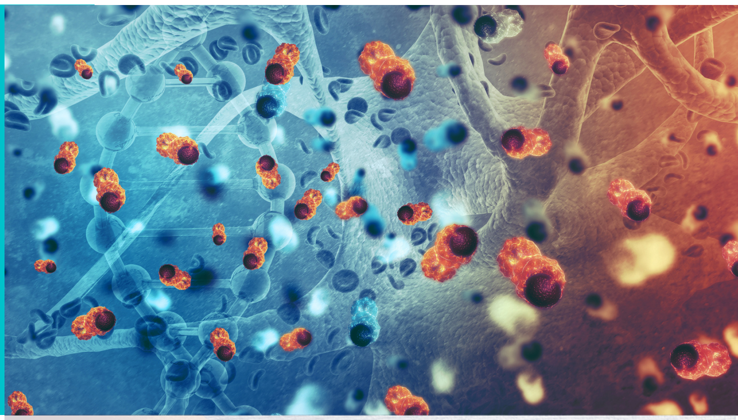
Cancer Research is one of the five missions of the new EU Framework Programme - Horizon Europe.

Demographic drivers of increasing world population size, life expectancy and aging population (particularly in higher-income countries), along with the progress against many other causes of death, implies that **the total number of cancer deaths continues to increase.** The expectation is an increase to 27.5 million new cases and 16.3 million deaths by 2040.

Source: Globocan, 2018

OBJECTIVES AND BENEFITS

The current research in the SEE region tends to be fragmented, with a lack of collaboration and common strategic vision. The SEE region as a whole is lacking a large-scale competitive infrastructure to be placed on the roadmap of the European strategy, in line with the EU research priorities.



SEEIIST is committed to:

Provide access to an innovative particle cancer therapy, for the first time in the SEE region.

Develop a sustainable multidisciplinary and collaborative network of clinicians, medical physics, physics, computer experts and engineering profiles in order to optimise the progress in cancer research and therapy to benefit all Europe.
The growing community will benefit by fostering a joint excellent research programme in the spirit of "Science for Peace".

Foster collaboration among all relevant stakeholders such as hospitals, universities, policymakers and industry, enabling rapid translation of research to the optimal treatment of cancer patients.

Implement the first of a kind Pan-European research infrastructure, with 50% of the beamtime dedicated to patient treatment and 50% to multidisciplinary research.

The SEE region will benefit from the **CERN model,** which succeeded in re-unifying the European countries and reverting the brain-drain that occurred after the Second World War, becoming a global leader of excellence.

Inspired by the successful models of **CERN followed by SESAME,** SEEIIST is aiming to attract excellent scientists within and from outside the SEE region to do collaborative research.

SEEIIST will design and implement **Education and Training programmes to train future personnel** for the benefit of the growing number of PT facilities in Europe and beyond. Such programmes will help to mitigate or even revert the brain drain. SEEIIST will be linked to universities and academic institutes of the SEE region and will become an excellent partner for masters and PhD research.

REVERSE THE BRAIN DRAIN

South-Eastern Europe (SEE) is battling with a constant depletion of high skilled and talented people due to the lack of:

- Excellent Research
- Career Opportunities
- Perspective and Future

The **Global Competitiveness Index** is an indicator for the capacity of each country to retain talent. Results from the **World Economic Forum** in 2019 show that most of the SEE countries are facing a sky-high youth unemployment that drives emigration from the SEE region. As the young talent leaves, their homelands' **economic prospects** decline even further. The ranking shows that in particular young and talented people from SEE are deserting their home countries, seeking professional development and recognition of their talent abroad.

SEEIIST will offer research capacity to about **1000 researchers from and outside** the SEE region. These researchers will become users of the SEEIIST, pursuing innovation in particle therapy and jointly advancing current knowledge.

2019 country rating by capacity to retain talent

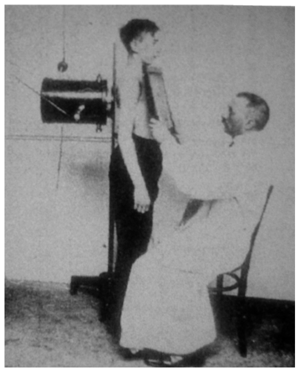
Rank in 2019	Country
1	Singapore
2	USA
3	Hong Kong
4	Netherlands
5	Switzerland
35	Slovenia
49	Bulgaria
59	Greece
63	Croatia
72	Serbia
73	Montenegro
81	Albania
82	North Macedonia
92	Bosnia and Herz.
139	Congo
140	Yemen
141	Chad

FROM RADIOTHERAPY TO PARTICLE THERAPY

X-RAY

1895

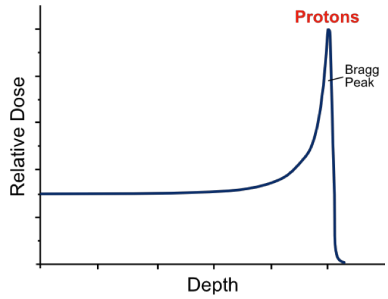
Photons (X-rays) are known to deposit the greatest part of the energy to the tissue at the entrance of the irradiated body. Even though the skin may not be the target, it receives the highest dose. However, accelerated charged particles such as protons, carbon and other heavy ions deposit the greatest part of their energy at the end of the range in the human body. The highest energy dose is delivered at the end of the range in the tissue.



BRAGG PEAK

1903

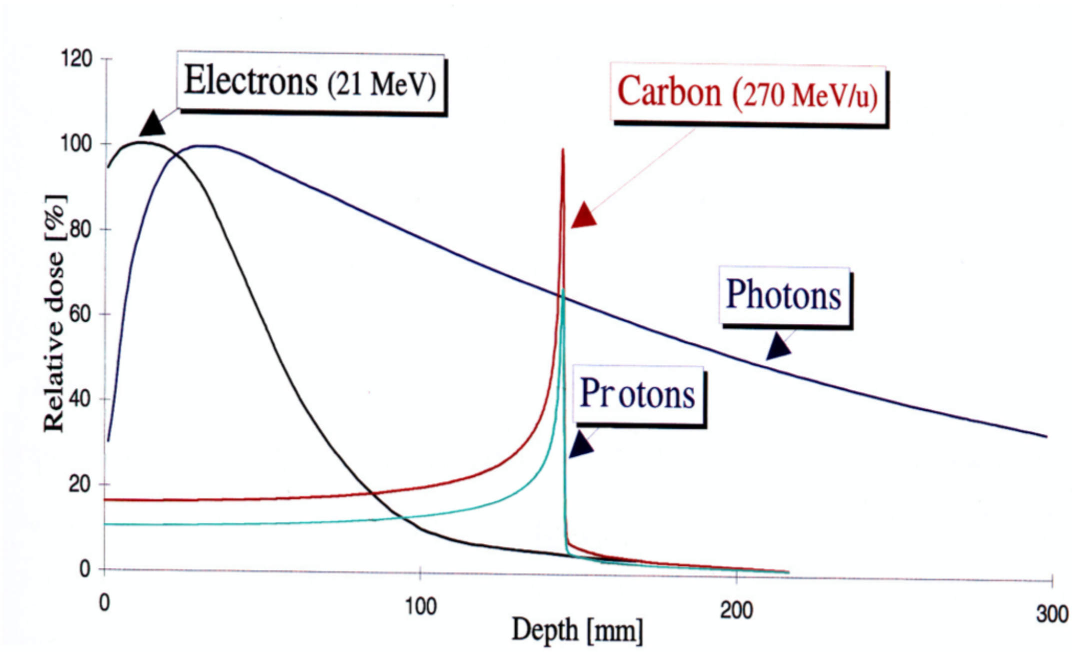
The range of the particles can be controlled so that the maximal energy (Bragg-peak) is deposited in the tumour volume, maximising the DNA damage and thus killing the cancer cells, protecting the healthy tissues.



PROTONS CAN BE USED CLINICALLY

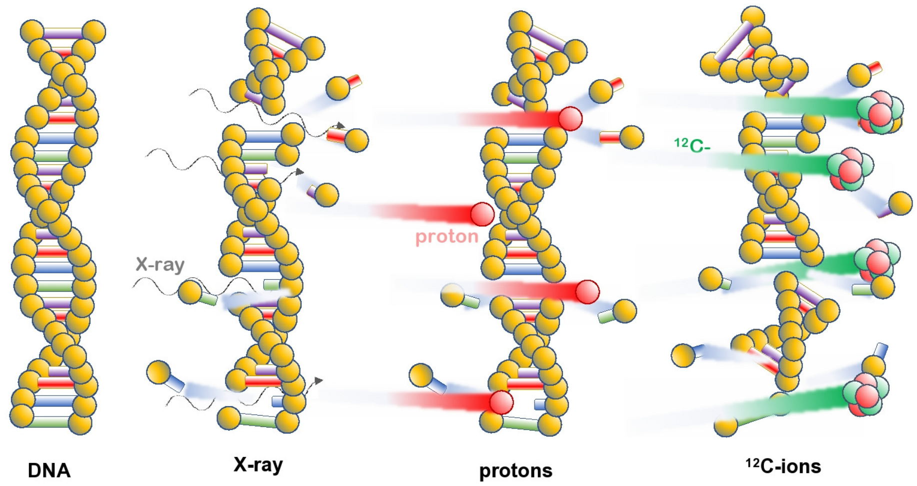
1946

As can be seen in the figure below, the accelerated carbon ions (red line) deposit even a higher dose in the targeted area compared to protons, carbon Bragg-peak is higher than that of the protons. Hence, the damage caused to the targeted tissue by heavier accelerated particles is much greater.



Depth in the body (mm)

BIOLOGICAL EFFECTS OF PARTICLE THERAPY



The **figure** on the left shows **the DNA damage** induced by photons (X-rays) and charged particles, such as protons or heavier ions (C-12). The damage caused by high energy photons used in conventional radiotherapy is much smaller compared to that of **protons and C-ions.**

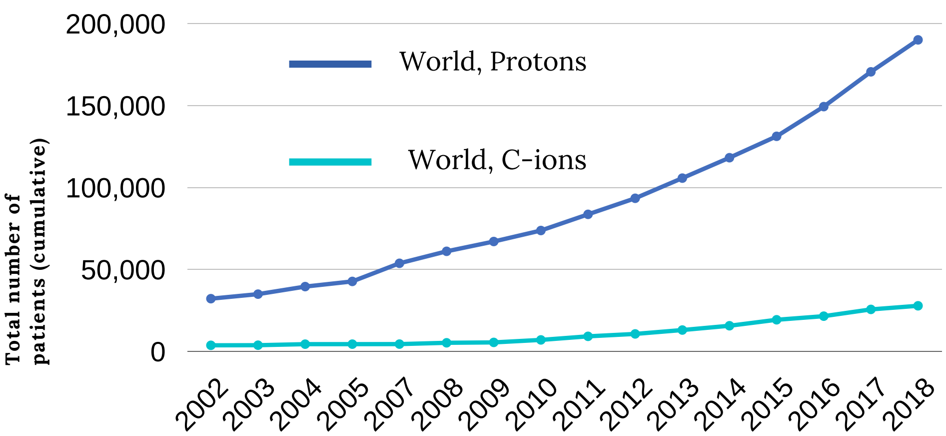
C-ions have even higher energy than protons and therefore induce more **damage to the DNA.** Experimental results and clinical studies show that the heavier the ion, the greater the extent of damage, and such damage is less readily repaired.

Particle Therapy is using the unique physical and radiobiological properties of charged particles, allowing highly conformal treatment of various kinds of tumours, especially those that are radio-resistant, including those that are inoperable and hard to treat .

To fully exploit the beneficial radiobiological properties of ion beams for particle therapy, a **research effort is needed for providing the required knowledge in cancer-related radio-biology and PT.** In addition, advanced research tools and methods are essential for providing innovative diagnostics and treatment plans to help clinicians in their decision-making for cutting-edge treatment. A systematic generation and collection of radiobiological data are needed to push the potential of particle therapy beyond the current limits.

By addressing the latest research challenges and opportunities in PT, SEEIIST aims to train the next generation of PT experts and thereby enable more effective and advanced cancer care, tailored to the needs of each individual patient, i.e. "personalised treatment", and thus improve the patients quality of life.

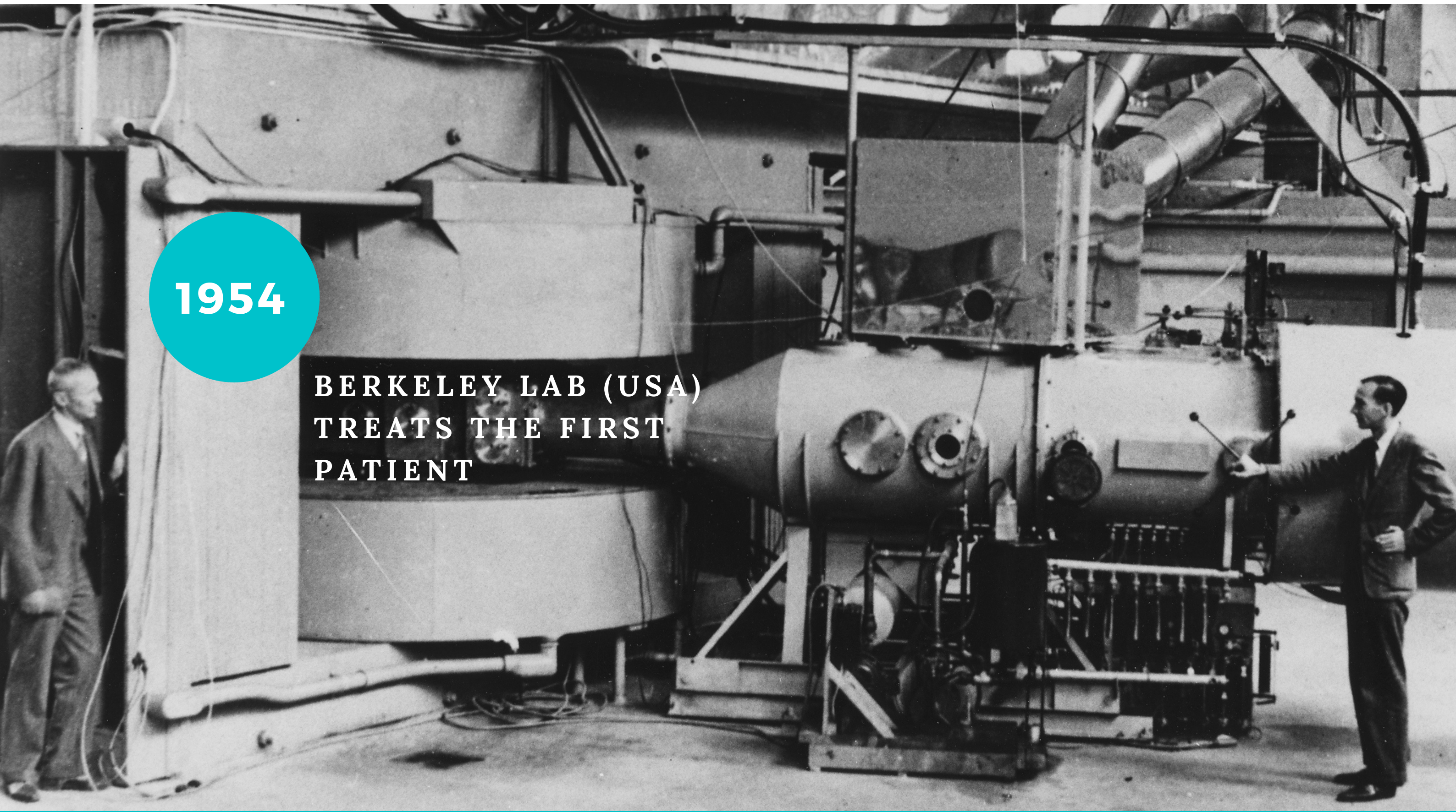
Patients treated with Protons and C-ions, worldwide



REF.: PTCOG, 2020

The figure above shows a rapidly increasing trend of the number of particle therapy patients treated with protons and C-ions worldwide.

MILESTONES OF PARTICLE THERAPY



1954

BERKELEY LAB (USA) TREATS THE FIRST PATIENT

The three years which made the difference in PT.
The knowledge was transferred from the laboratories to the clinics.

1990

In October 1990 the world's first hospital-based proton treatment facility at the Department of Radiation Medicine at Loma Linda University of California in USA began clinical investigations, using the world's first proton accelerator and clinical facility designed for treating patients in a hospital setting.

1994

In 1994 Carbon-ion radiotherapy was introduced for the first time at the National Institute of Radiological Sciences (NIRS) in Japan, with beams from the Heavy Ion Medical Accelerator in Chiba. The tumour sites with more than 200 treated patients include Prostate, Lung, Head and Neck, Bone and Soft Tissue, and Liver cancer. The experience of NIRS proved that carbon ion therapy is much more efficient for treating the so-called 'radio-resistant' tumours and difficult-to-treat tumours.

1997

In 1997 Carbon-ion radiotherapy was introduced for the first time in Europe at GSI, Darmstadt, Germany, treating over 400 patients before the start of the HIT facility in 2009 in Heidelberg. This facility is based on a totally active beam delivery and a biology-oriented treatment planning system in order to maximally exploit the favourable properties of particles.

FACILITY FOR CANCER THERAPY AND BIOMEDICAL RESEARCH

The experimental programme of SEEIIST tackles five main Research Areas:

Radiobiology – Pre-clinical radiobiology is an essential tool to support new therapy solutions

In-vivo studies – The majority of the radiobiology studies needs animal experiments

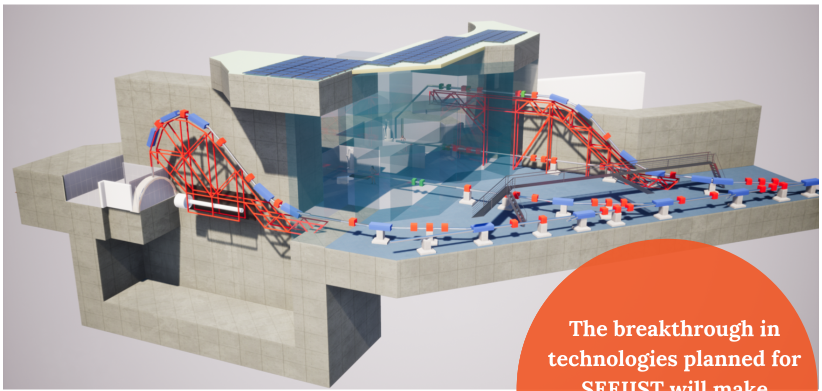
Medical physics – Ultra-fast dose delivery methods will extend ion therapy to the special group of tumours in moving organs

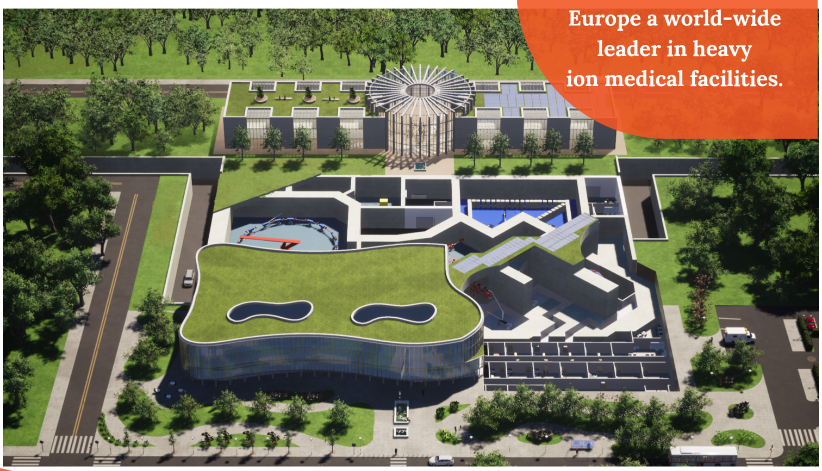
Clinical trials – As a Research Infrastructure, all the patients treated will be enrolled in research clinical trials

Material science – Innovative material research using high-energy ions (radiation hardness, space microelectronics, nanotubes...)

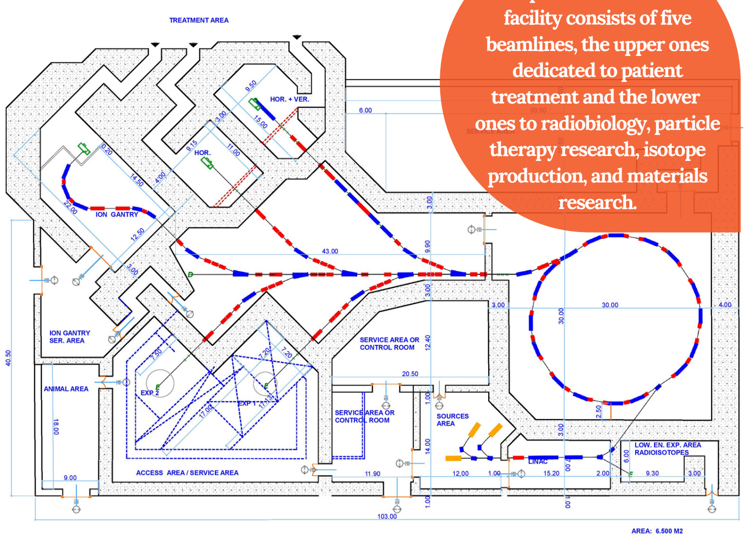
Radioisotope production – Many isotopes for medical applications (diagnostics and cancer treatment) can be produced by the novel Injector-Linac

Approximately ***400 patients*** per year will be treated as indicated for a population of about 20M. In parallel, **the rest of the beam** time will be dedicated to biomedical research with multi-ion sources beyond presently used proton and carbon-ions, **making the SEEIST project unique in the world.** SEEIST will host **about 1000 researchers**, including a large number from outside the SEE region.





The breakthrough in technologies planned for SEEIIST will make Europe a world-wide leader in heavy ion medical facilities.

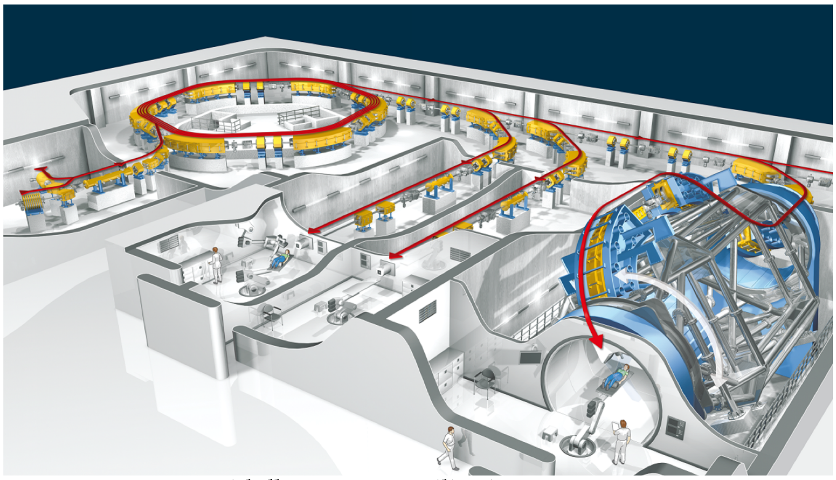


The preliminary footprint of the SEEIIST facility consists of five beamlines, the upper ones dedicated to patient treatment and the lower ones to radiobiology, particle therapy research, isotope production, and materials research.

Experimental rooms will be furnished with **movable shielding walls** for dividing the experimental space according to the needs of the experiments.

SEEIIST will host **fundamental and clinical research** that utilises proton and heavy ion beam intensities beyond the ones currently used, thus making the SEEIIST project unique in the world.

INNOVATIVE ASPECTS OF THE SEEIIST DESIGN



Heidelberg HIT Facility in Germany

- The SEEIIST design is inspired by the advantageous and successful solutions developed for **HIT, CNAO, MedAustron.**
- **SEEIIST** will implement all the positive features of the existing EU centres, but make them even more effective, safe, patient and environment friendly, including improved awareness for recycling and promoting carbon-clean technologies such as renewable green energy using solar and wind power.

New rotating gantry design with advanced superconducting technology and significantly compact in size.

New Accelerator Design with Outstanding Beam Intensity, up to 2 x 10^{10} accelerated C-12 ions, 20 times higher than that of the present European centres and the record intensity in Japan.

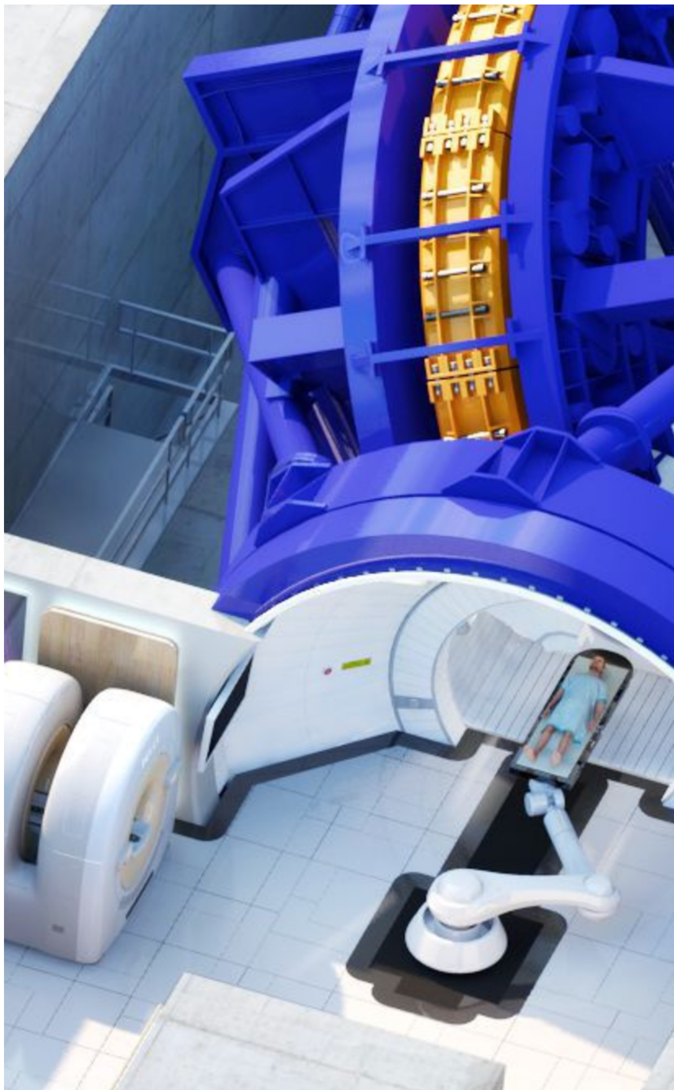
FLASH therapy, fast extraction and shaping of the beam with 100-1000 times larger dose rates than that of standard treatments.

Availability of internal and external animal facilities, allowing extensive research programs which need in-vivo irradiation.

Flexibility in serving the needs of broad experimental research, covering the range of new treatment modalities and providing different ion species, from protons to argon.

Flexible Dose Delivery system, delivering the standard “slow extracted beam” to perform active tumour painting, an effective dose delivery of >50 Gy/s for research purposes and eventually for the so called FLASH treatment (irradiation with short-high intensity beams).

Synchrotron injector designed to be easily converted to a high duty cycle linac for the production of radioisotopes for imaging and the treatment of metastatic tumours.



NETWORKS AND HUBS

SEEIIST NETWORKS

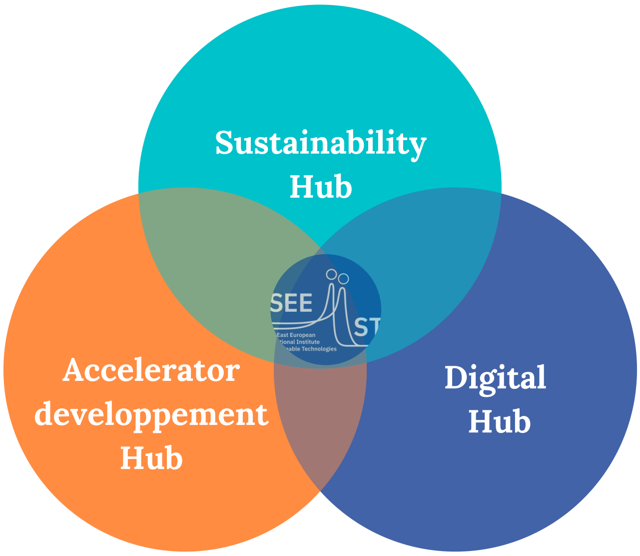
The **Scientific Network**, the **Clinical Network** and the **Veterinary Network** will connect the groups to establish and construct the facility and to perform research within the scope and principles of an open access facility.

SEEIIST will provide durable **open-access platforms for knowledge exchange** among the relevant stakeholders (researchers, doctors, engineers, technicians and policy makers), open new research topics and strengthen scientific capacities through hands-on training.

SEEIIST - AN OPEN-ACCESS INFRASTRUCTURE WITH INNOVATIVE SOLUTIONS

Compact design, construction and operation costs lower by more than 30% with respect to current facilities.

"Green" concept of SEEIIST - SEEIIST will be designed to be energy efficient, safe, patient friendly, environment friendly, promoting recycling culture and solar PV/wind powering. It will promote carbon-clean technologies in line with the European Green Deal Roadmap set up by the EU President Ursula Von der Leyen to make Europe the first **climate-neutral by 2050.**



SEEIIST HUBS - OPPORTUNITY FOR THE SEE COUNTRIES

Three Hubs will be connected to SEEIIST, one devoted to the development of **components for the particle accelerator**, one dedicated to **sustainable energy production** required for running the facility and a **digital hub** to store and manage the large amount of data.
Since there will only be one site for the main facility, the **hubs will be distributed in the other countries of the SEE region.**

SEEIIST is fully aligned with the European Commission Policy on Green Deal & Horizon Europe Cancer Research Mission.

WHAT CAN WE DO BETTER FOR THE PATIENTS?

SEEIIST will offer hope to patients who cannot be successfully treated for certain indications by current methods.

Types of tumour with highest priority for proton therapy:	Types of tumour with highest priority for ion therapy (such as carbon):
• Adult skull base tumours. • Adult unresectable or relapsing meningioma. • Other rare adults' 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,chondrosarcomas of skull base, spine. • Soft tissue sarcomas of low, medium grade.
Total: about 80 cases/year for 10M inhabitants	**Total: about 200 cases/year for 10M inhabitants**

Let scientists lead in rebuilding bridges and make innovative particle therapy accessible for the citizens of the SEE region.

- Results show that particle therapy is more effective than conventional radiation therapy for treating inoperable, paediatric and tumours close to critical organs as well as deep-seated and radio-resistant cancers. **About 400 priority patients per year** will be treated in SEEIIST, based on a 50% fraction of the beamtime.

- SEEIIST will treat patients with protons and heavier ions with the highest beam intensities world-wide. The new knowledge in physics and radiobiology will optimise the treatment with **combined modalities such as FLASH and immunotherapy, leveraging also the research in radiogenomics.**

- SEEIIST will take advantage of the newly developed detection devices such as **prompt gammas,** and imaging with **PET/CT** for patient positioning, dose verification and follow up.

IMPORTANT POLITICAL AND SCIENTIFIC SUPPORT FOR SEEIIST

EUROPEAN COMMISSION

The Directorate General for Research and Innovation (EC DG-RTD) provided the first direct financial support of 1M EUR in 2019 to start the **SEEIIST Design Phase.** The finalisation of this Phase has been assured by the successful application to the highly competitive EU H2020 Call - INFRAIA-2020 in late 2020 for the **HITRI*plus*** project with an additional 5M EUR. A strong consortium of 18 renowned European Research Institutes from 14 countries and additional institutions from the SEE Region supports SEEIIST in this context.

For the longer-term perspective, an application entitled **SEEIIST@ESFRI Roadmap 2021** including a pre-TDR has also been submitted in late 2020. The project has received strong political support from 9 West- and South-Eastern-European countries as well as from CERN and from TIARA. The Pan-European dimension associated with the SEEIIST Project will allow the use of structural funds in the future.

SEEIIST is now explicitly part of the Economic Investment Plan for the Western Balkans through the Innovation Agenda.

FDFA SWITZERLAND

The Swiss Government has offered political support to develop a **Science Diplomacy Roadmap** for SEEIIST. The central parts are two-fold. The Swiss Federal Department of Foreign Affairs (FDFA) will support SEEIIST to develop an optimal form of a full-term international legal entity, based on past experience as well as on the most recent developments in this area. It will also patronise the delicate process of the final site selection for the Institute among the SEE Member States.

CERN

The European Organization for Nuclear Research - host of the development of the medical accelerator design.

GSI-FAIR

Facility for Antiproton and Ion Research – host of the biophysics research group.

IAEA

International Atomic Energy Agency - supports the Capacity building program (RER project of EUR 0.5 million for training young scientists from SEE region).

Support by many other institutions such as TERA, HIT, CNAO, PSI, INFN, ENLIGHT and others.

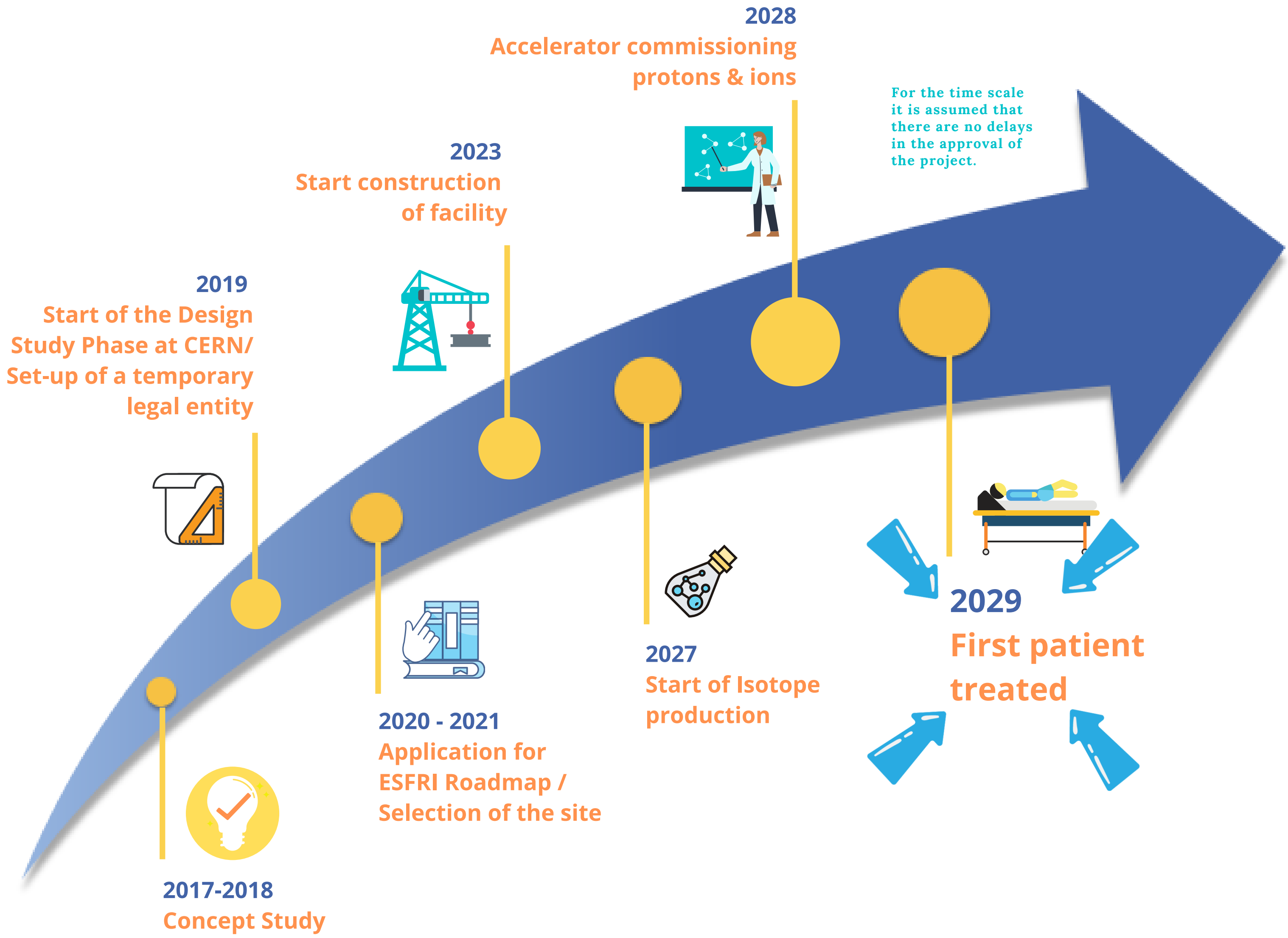
240 million

required for SEEIIST, guaranteeing competitivity in Europe. Multiple sources of financing are necessary : EU Structural and cohesion funds, IPA funds, some contributions from member-states and other funds.

TIMELINE

THE MISSIONS OF SEEIIST:

COMBATING CANCER
SCIENCE FOR SOCIETY
SCIENCE FOR DIPLOMACY
BREAKTHROUGH IN TECHNOLOGY



No matter where the SEEIIST facility will be located, the entire **SEE region will have enormous benefit from it.**

After careful considerations and evaluations of different criterias, the site selection will be completed by end of 2021.