

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

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**SEEIIST**  
**WWW.SEEIIST.EU**

*South East European  
International Institute for  
Sustainable Technologies*



December 2020





Map showing SEEIIST Member States



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 the first official political support by the Government of Montenegro, initiated by **the former Minister of Science, Dr. S. Damjanovic in March 2017**. Around the same time, it has been proposed for adoption the main direction of the project – the construction of a pan-European Research Infrastructure for Cancer Therapy and Biomedical research with ion beams. Later that year, a first Conceptual Design Report on a possible SEEIIST facility for cancer therapy has been presented. 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, Croatia (ad referendum), Kosovo\*, Montenegro, North Macedonia, Serbia and Slovenia at a Ministerial meeting held at CERN. Greece took an observer status.

The Declaration of Intent was followed by a **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**.

\* '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 **SEEIIST region** with a total population of about 40 million has no facility for PT.



Multidisciplinary  
Research with a  
Breakthrough  
Technologies

State-Of-The-Art  
Cancer Treatment

Collaboration  
through Science  
Diplomacy

## COMBATTING CANCER

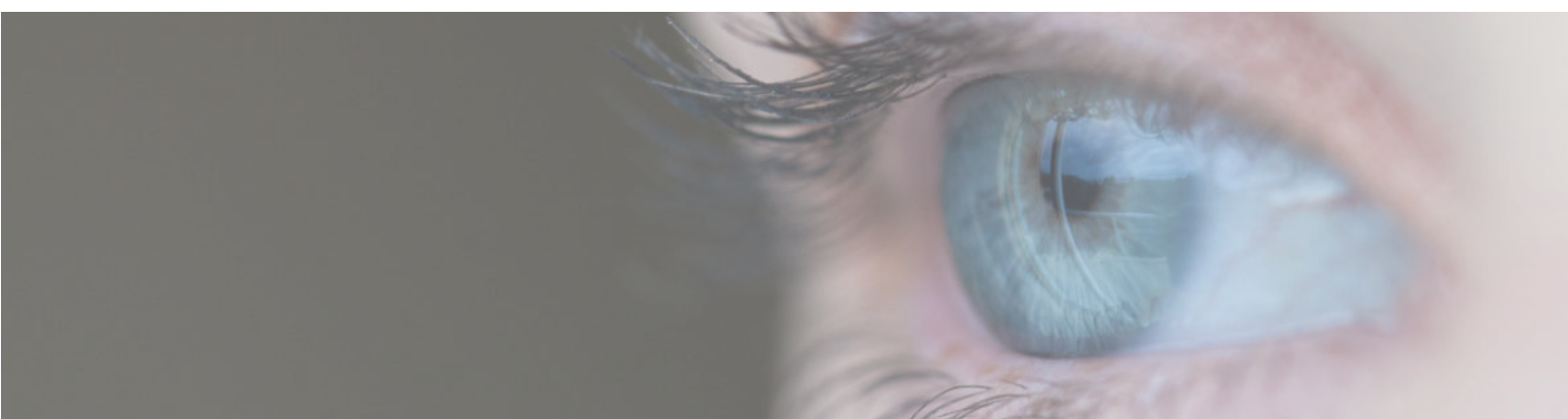
- **The SEE region** needs a common state-of-the-art infrastructure to promote a Pan-European collaboration and excellent research on advanced cancer treatment for the benefit of its citizens.

## VISION

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

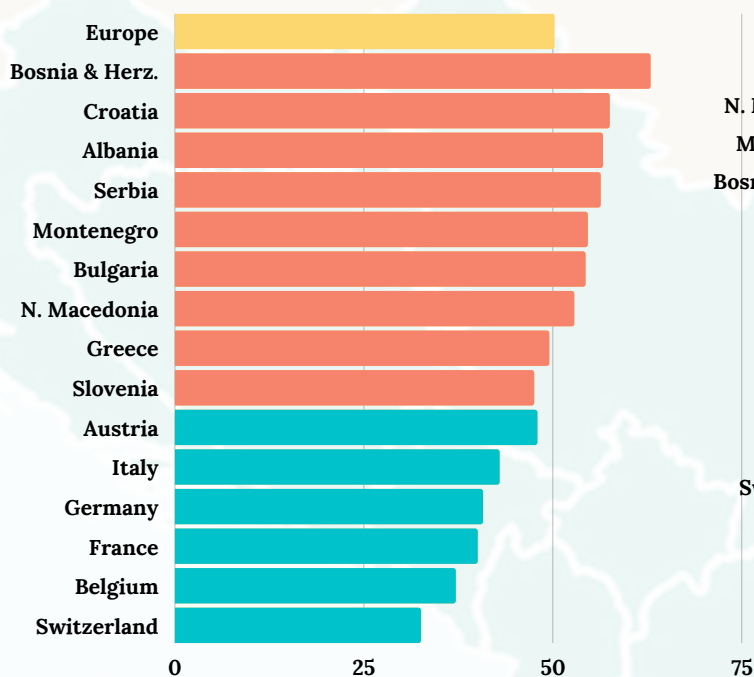


# CANCER SCENE IN SOUTH EAST EUROPE

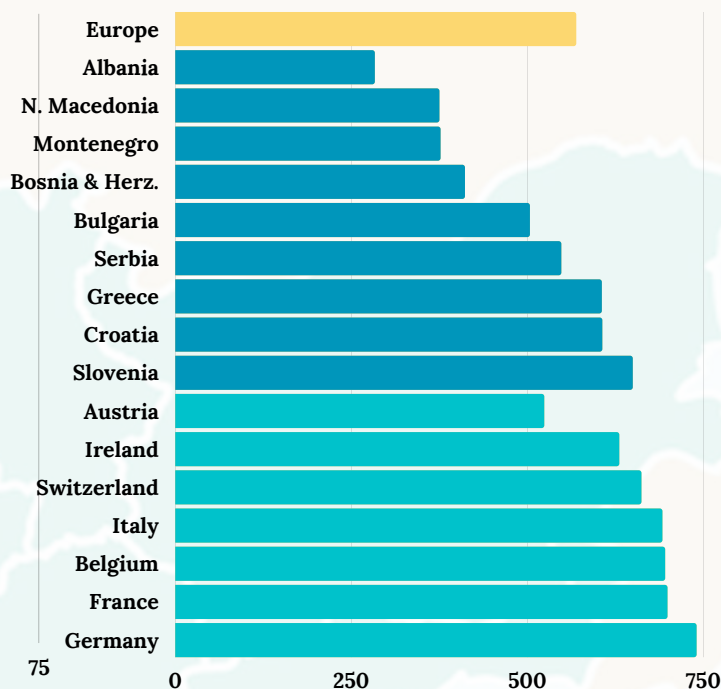
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The SEE countries are facing more challenges compared to Western Europe in combating cancer because of the lack of modern early diagnostic tools and state-of-the-art treatment.

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



**Cancer Incidence  
Cases in 100'000, Both sexes**



**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.**

**43 M**

**Total Population  
of SEEIIST countries**

**1000**

**New cancer cases in  
children for 2018 in  
SEEIIST countries,  
ages 0-14**

**222 000**

**Number of new cancer  
cases in SEEIIST countries  
for 2018 (all ages, both sexes)**

**120 000**

**Number of cancer  
deaths in SEEIIST  
countries for 2018**

**2,3 M**

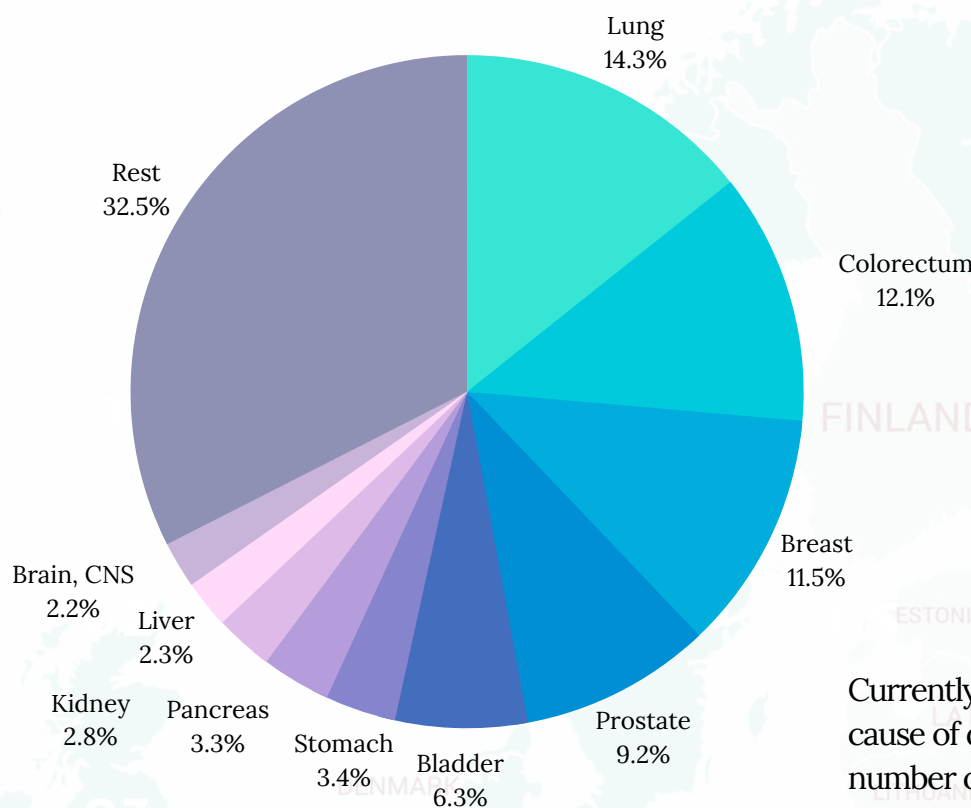
**New cancer cases  
in Europe for 2018  
(all ages, both sexes)**

**243 000**

**Projected number  
of new cancer cases  
in SEEIIST countries  
for 2030**



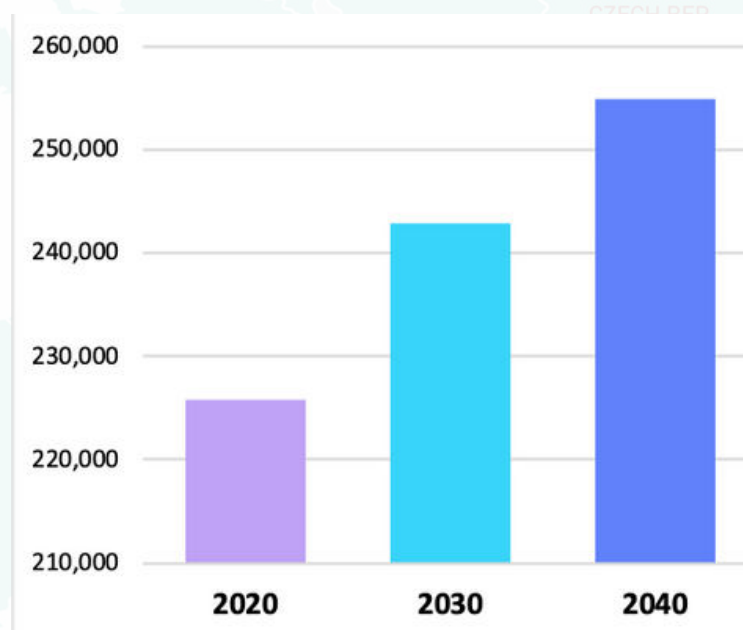
## Estimated incidence in SEE region by cancer type, all ages, both sexes (2018)



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
<b>TOTAL Number</b>	<b>222 315</b>

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.

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

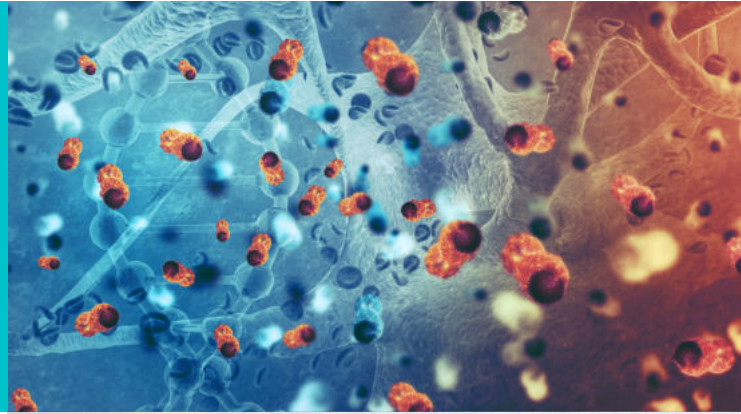


Currently, cancer is the second leading cause of death and it is projected to become number one in the coming years. **The battle against cancer** is a top priority for our society. In particular, there is an urgent need to develop cancer therapies that can cure difficult cases.

## 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**.

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 physicists, physicists, 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 multi-disciplinary research.

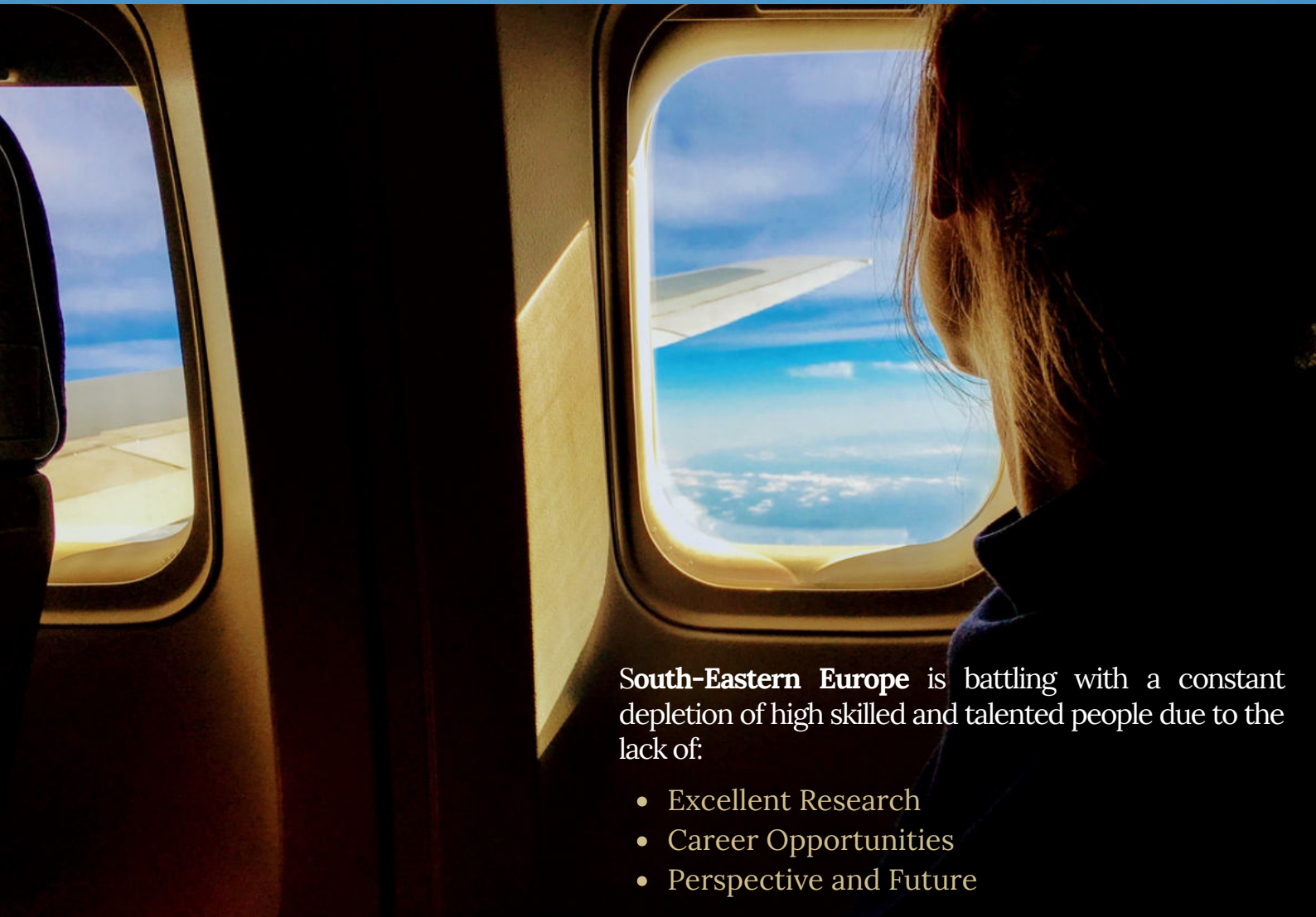
The SEE region will benefit from the **CERN model**, which succeeded in re-unifying the European countries and reverting the brain-drain that occurred after the Second World War, becoming a global leader of excellence.

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 Particle Therapy 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 training and conducting research by masters and PhD students.







**South-Eastern Europe** 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 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

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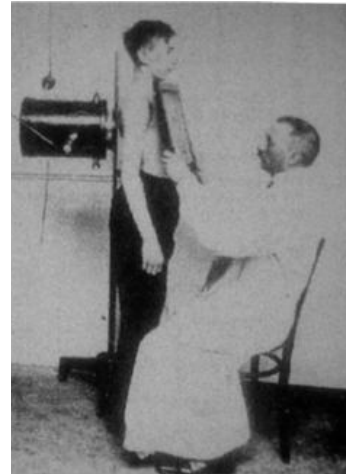
X-RAY

## 1895

FIRST PATIENT  
TREATED WITH  
PROTONS AT  
BERKELEY LAB (USA)

## 1954

X-rays are a type of radiation that can pass through the body. Photons called X-rays (when they are produced by electron interactions) 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.

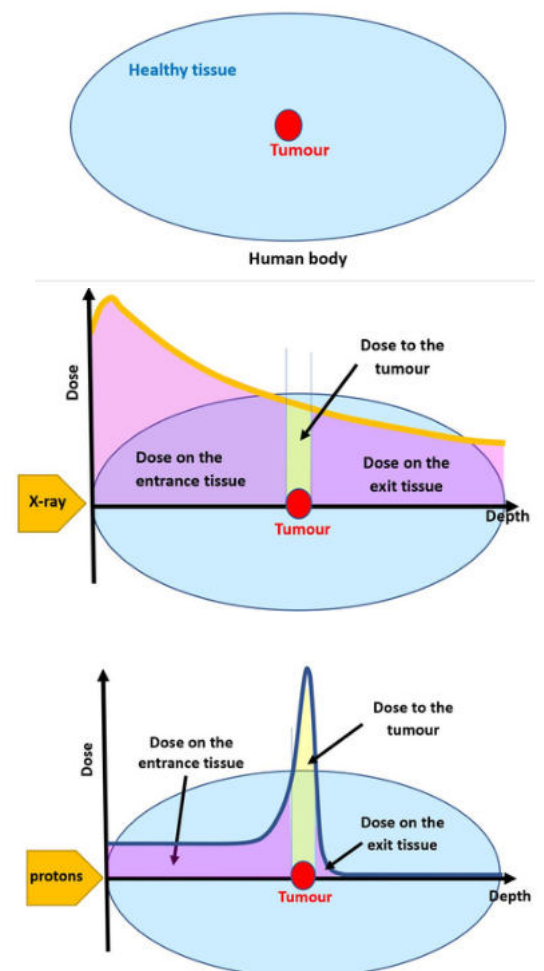


The ions used for particle therapy are produced from atoms by removing all or some of their electrons. These positively charged particles are accelerated in machines called accelerators to speeds close to the speed of light. A beam of such particles is then guided by electric and magnetic fields to enter the human body and destroy the cancer cells.

The picture on the right shows a figure of a human body (patient) with a tumour: Healthy issue (**blue ellipse**) with a tumour inside (**red circle**).

When the patient is treated using classical radiation therapy with **X-rays entering the body** from left to right, the dose delivered to the tumour is shown in yellow and the dose to the healthy tissue in purple. It can be seen that the healthy tissue will receive a higher dose than the tumour.

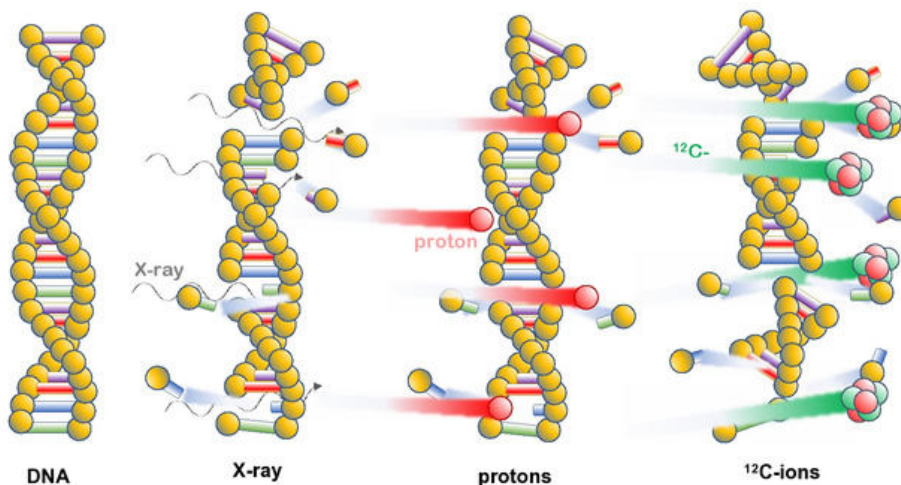
When the patient is treated using particle therapy with **protons**, or other heavier ions, such as carbon or oxygen, entering from left to right, the dose delivered to the tumour is shown in yellow. Clearly, the patient's healthy tissue receives a smaller dose (purple area) than with X-rays.





# BIOLOGICAL EFFECTS OF PARTICLE THERAPY

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The damage caused on the DNA by **protons** and **C-ions** is much larger compared to high energy photons (x-rays) used in conventional radiotherapy, as it is schematically shown in the left hand-side figure.

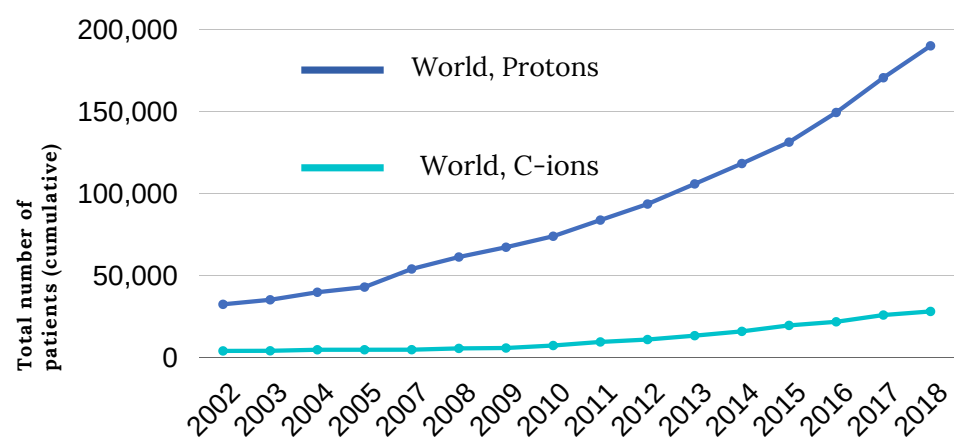
C-ions deposit higher energy than protons and therefore induce more **damage to the DNA**. Experimental results and clinical studies show that the heavier the ion, the greater the damage, and such damage is less readily repaired.

**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 difficult 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 radiobiology 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. Both 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 patient's quality of life.

**Patients treated with Protons and C-ions, worldwide**



REF.: PTCOG, 2020

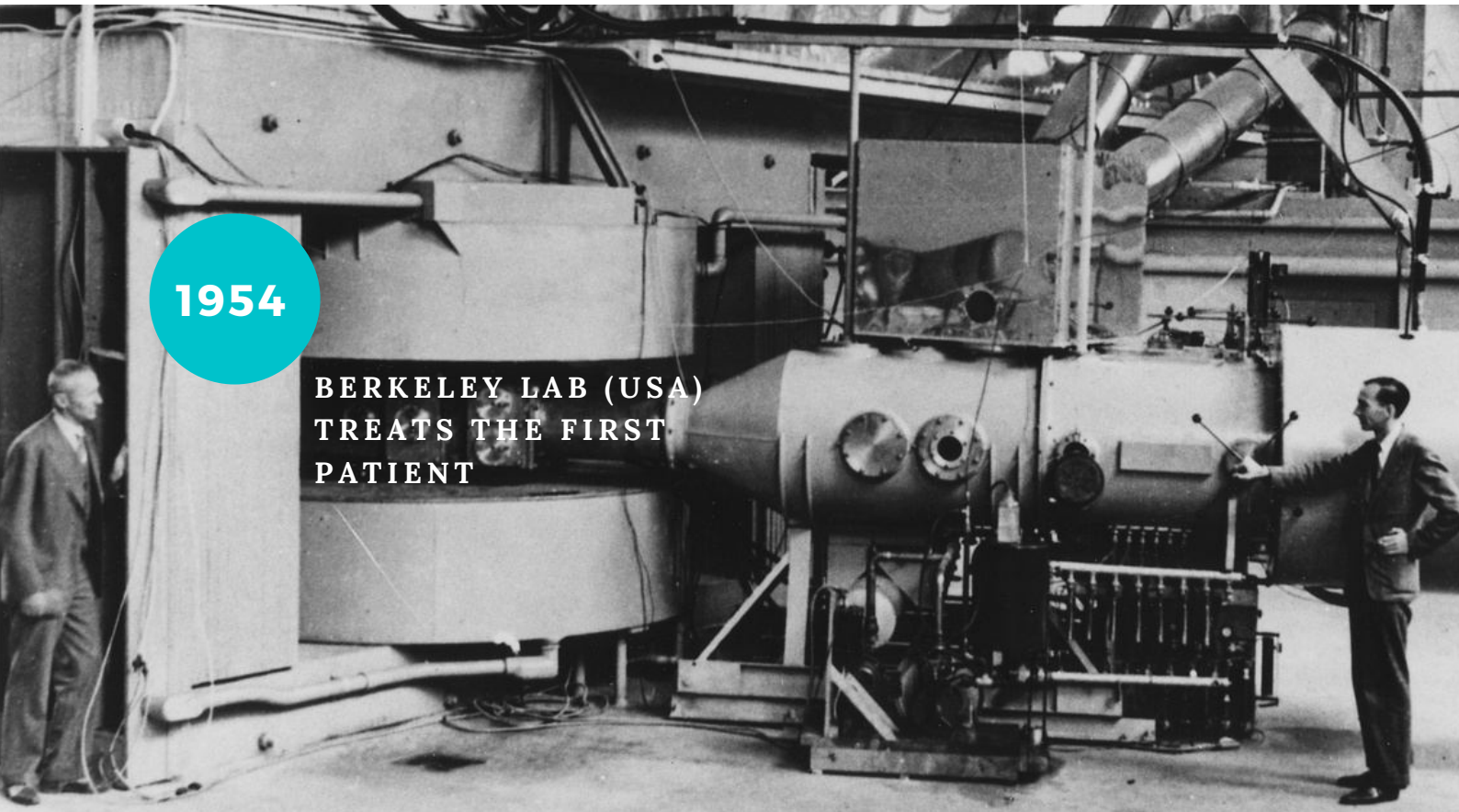
The figure above shows a rapidly increasing trend of the number of particle therapy patients treated with protons and C-ions worldwide.

# MILESTONES OF PARTICLE THERAPY

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1954

BERKELEY LAB (USA)  
TREATS THE FIRST  
PATIENT



The three years that 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 the USA began clinical investigations, using the world's first proton accelerator and a clinical facility designed for treating patients in a hospital setting. The 70–250 MeV proton synchrotron has been developed by Fermi National Accelerator Laboratory (Fermilab).

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

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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 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 (Linear Accelerator)

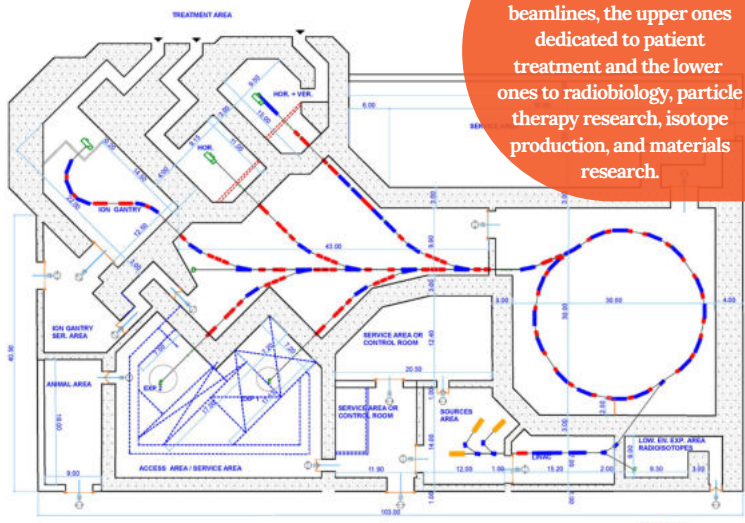
Approximately **400 patients** per year will be treated as indicated for a population of about 20M. In parallel, **the rest of the beam time** will be dedicated to biomedical research with multi-ion sources beyond presently used proton and carbon-ions, **making the SEEIIST project unique in the world**. SEEIIST 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.

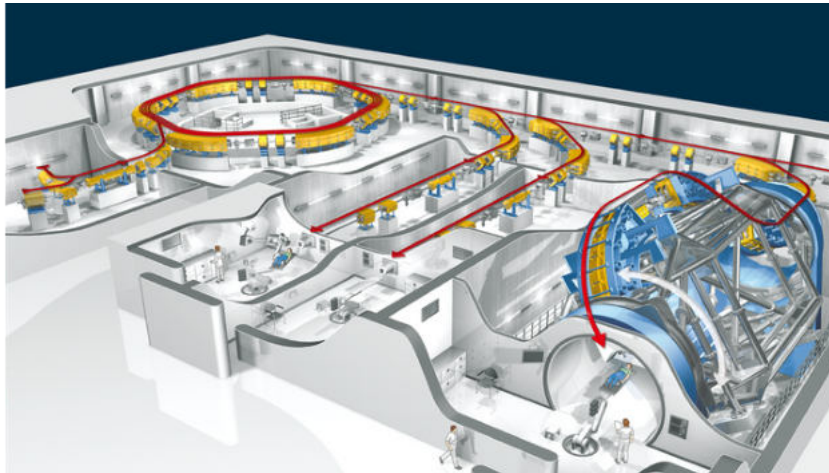


Experimental rooms will be furnished with **movable shielding walls** for dividing the experimental space according to the needs of the experiments.

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

# INNOVATIVE ASPECTS OF THE SEEIIST DESIGN

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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 significant reduction in size.

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

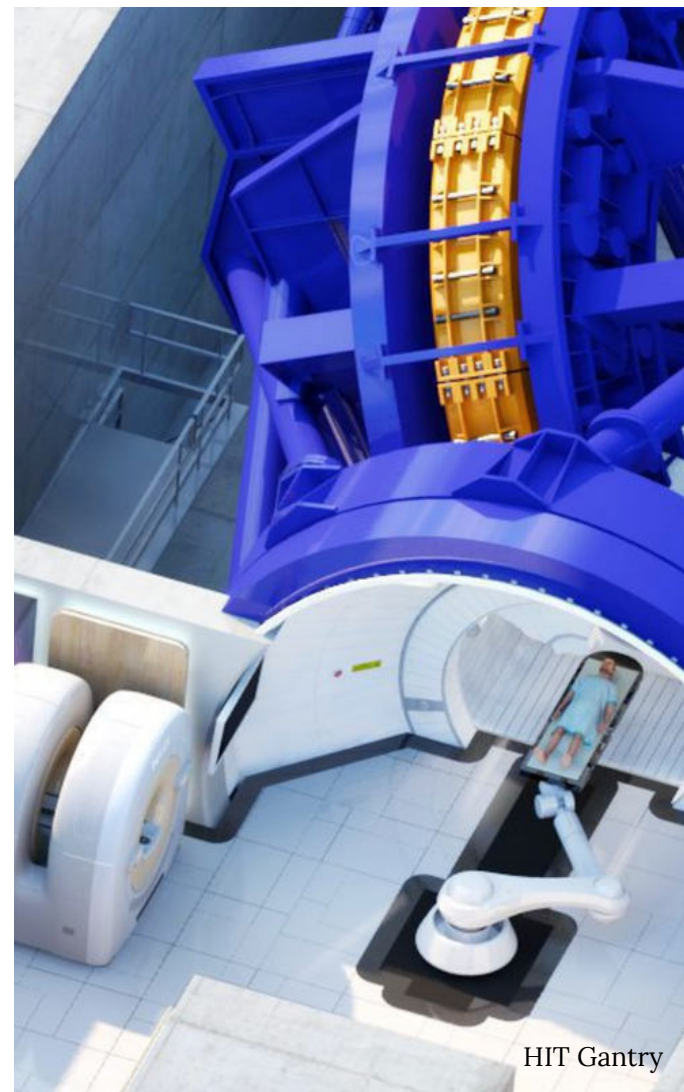
**FLASH therapy**, fast extraction and shaping of the beam with 100-1000 times larger dose rates than that of standard treatments.

**Availability of internal and external veterinary 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 linear accelerator (linac) for the production of radioisotopes for imaging and the treatment of metastatic tumours.



HIT Gantry





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

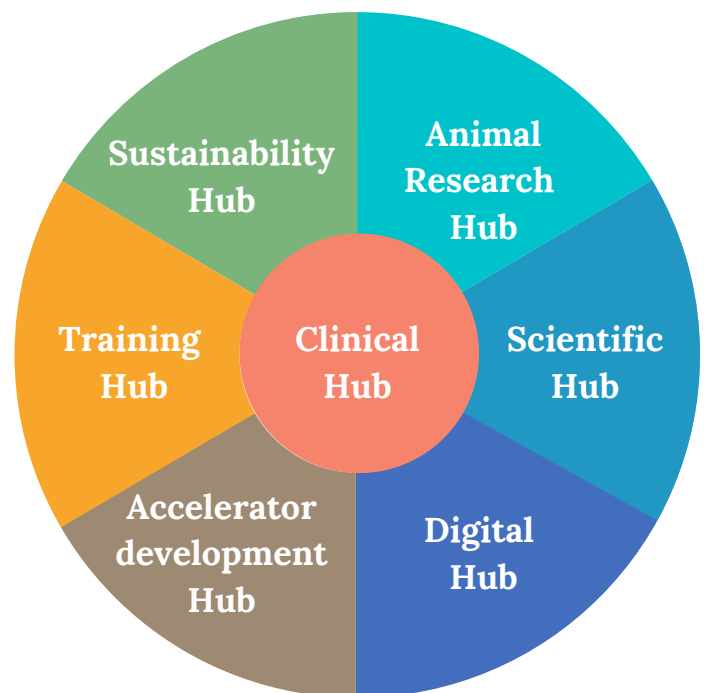


SEEIIST is fully aligned with the European Commission Policy on Green Deal & Horizon Europe Cancer Research Mission.

## SEEIIST NETWORKS

The **Scientific Network**, the **Clinical Network** and the **Veterinary Network** will connect the groups to establish and construct the facility and 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 HUBS - OPPORTUNITY FOR THE SEE COUNTRIES

Hubs will be connected to SEEIIST, three scientific, three technical 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**.

# WHAT CAN WE DO BETTER FOR THE PATIENTS?

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

## Types of tumour with highest priority for proton therapy:

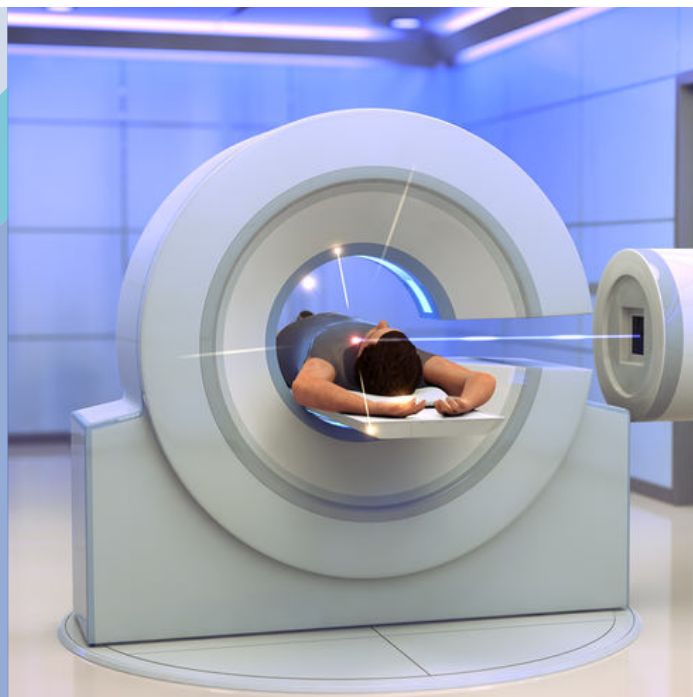
- Adult skull base tumours.
- Adult unresectable or relapsing meningioma.
- Other rare adults' central nervous system tumours.
- Child central nervous system tumours.
- Any other child solid tumours.

**Total:**  
**about 80 cases/year/**  
**10M inhabitants**

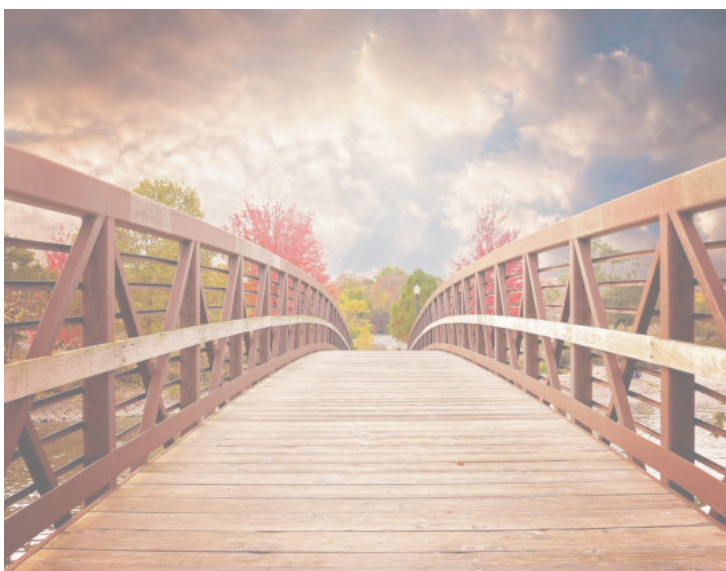
## Types of tumour with highest priority for ion therapy (such as carbon):

- 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 200 cases/year/**  
**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 produced so far. 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

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## 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 **HITRIplus** 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. FDFA will oversee the delicate process of the final site selection for the Research Infrastructure in the SEEIIST Member States.



## CERN

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

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



## GSF-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).

Acknowledgement: Thank you to our collaborators and reviewers from CERN, GSI, HIT, ENLIGHT, TERA foundation and SEEIIST for their contribution to this document. A special thank you to Dimitris Kaprinis for his creative design of the facility shown on the cover.

# 240 million

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

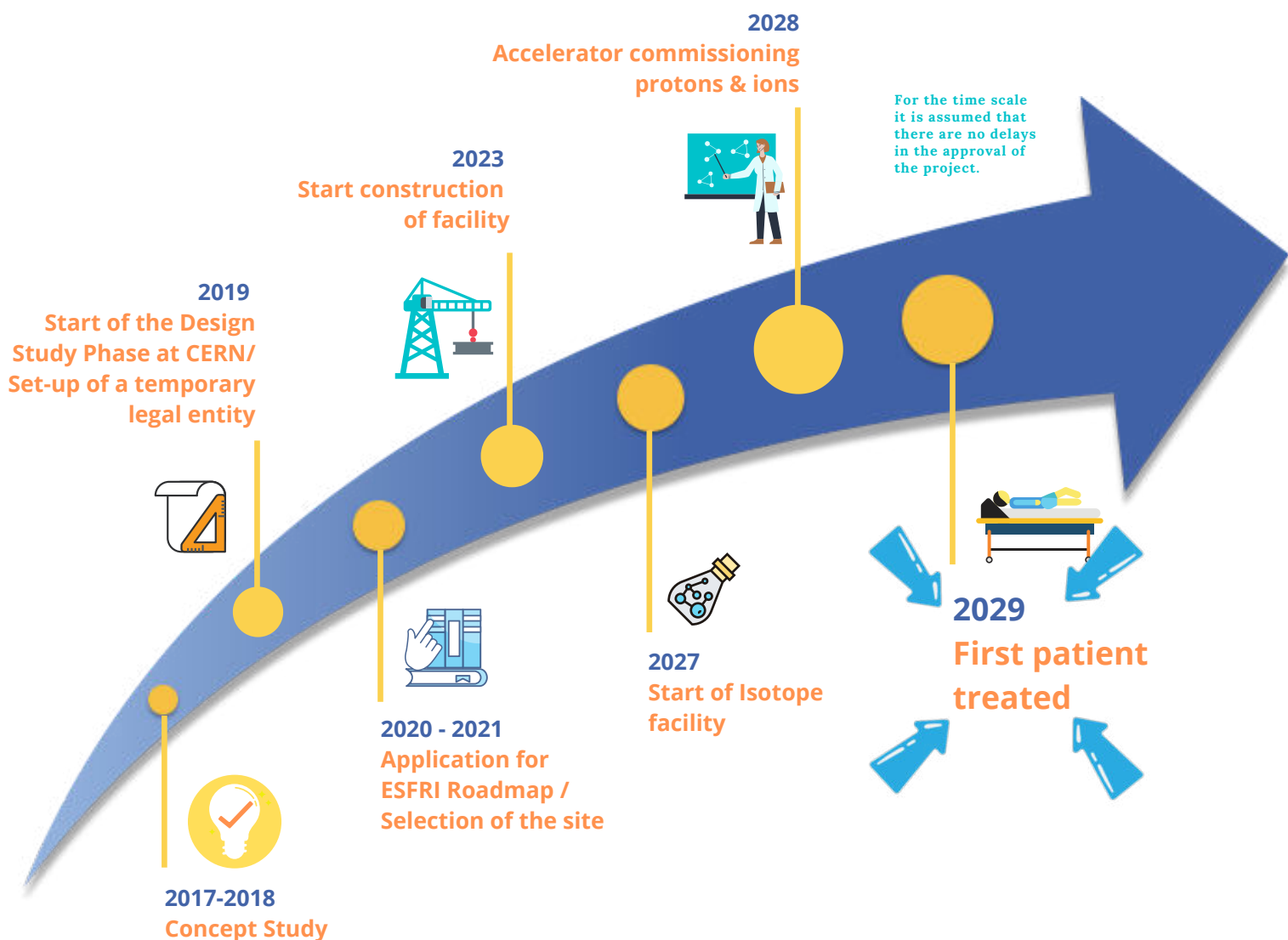
## THE MISSIONS OF SEEIIST:

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 benefit greatly.**

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