

Beating Cancer with SEEIIST while shaping Science in South-East Europe

SEEIIST



South East European International
Institute for Sustainable Technologies
<https://seeiist.eu>

Physics Matters – On-line Colloquium 29 August 2024

Dr. Sanja Damjanovic, GSI Helmholtz Centrum for Nuclear Research, Darmstadt, Germany

Science Diplomacy

Global Research projects show what mankind is able to achieve when working together coherently towards a common goal

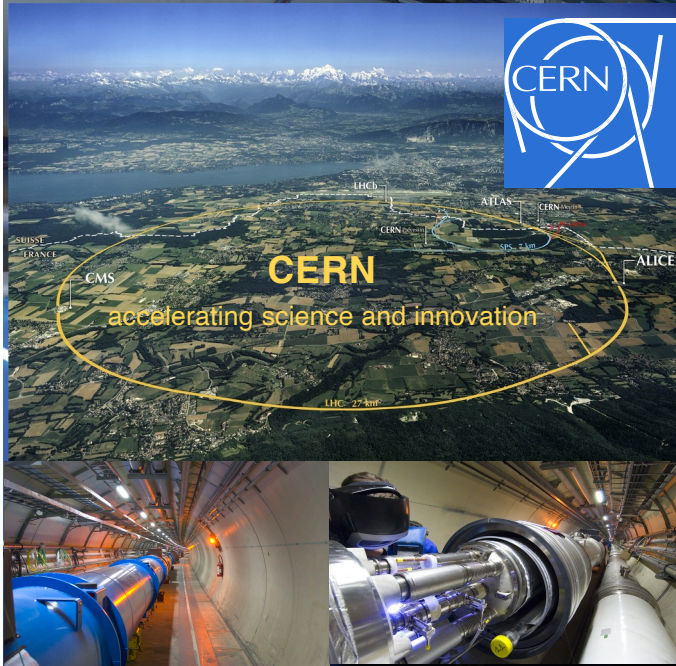
Power of Science Diplomacy - 'Science done by many nations' – key example CERN

Research Infrastructures

proven to have a powerful social and economic impact as a multinational venture, helping solving global challenges as powerful neutral tools with the mission of 'Science Diplomacy'

LHC@CERN the largest scientific instrument ever built - symbolizing global cooperation

Science Diplomacy >>> Driver for SEEIST



After CERN in Geneva and SESAME in the Middle East
SEEIST is yet another concrete example of Science Diplomacy





How it started?

Official launch: Government of Montenegro initiated SEEIST in March 2017



MONTENEGRO

Minister of Science

Dr Sanja DAMJANOVIĆ



Background: After 20 years working at CERN
Minister of Science of Montenegro from Nov.
2016 to Dec.2020

Rapid convincing: Secured Government support
just in 3 months

Leadership Role: Appointed as a political lead
to setup SEEIST's scientific framework

Missions of the SEEIST project

- ❖ **Promote collaboration:** bridge science, technology and industry for regional advancement
- ❖ **Revive tradition:** recover the great tradition in technology which SEE had in the past
- ❖ **Address Brain Drain:** Slow down or even revert the exodus of talents
- ❖ **Foster Regional Cooperation:** Mitigate tensions between the countries in the region
- ❖ **Break New Ground:** Interrupt 70 years period without building any new large-scale research infrastructure based on new technologies
- ❖ **Leverage EU support:** Utilize EU cohesion funds and the Global Gateway through the Economic and investment plan for the WB

These goals can only be achieved through a pan-European large-scale RI grounded in the latest technologies

EC's backing and support for SEEIIST – Highlighting Key Endorsements, Leadership and Vision, and Scientific impact

SCIENCE BUSINESS

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Montenegro's research minister wants to heal war wounds with science

31 Oct 2019 | News

R&D Policy

Research infrastructures

A new large-scale research infrastructure will revive the scientific and technological potential of the Balkans, whilst helping its economy and bringing people together around a shared endeavour

By Florin Zubaşcu



A multidimensional aspects of SEEIIST were quickly recognized by the European Commission, leading it to the first financial support in 2019

SCIENCE BUSINESS

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Viewpoint: Peace and prosperity should be end goals of scientific collaboration

31 Oct 2019 | Viewpoint

R&D Policy

Horizon Europe

Science diplomacy can work when other kinds of politics and diplomacy have failed, says Carlos Moedas, outgoing commissioner for research and innovation

By Carlos Moedas



Building bridges through science

As with SESAME, the same great potential is plain to see in numerous places at both an international and regional level. One case in point is the Southern Eastern European International Institute for Sustainable Technologies (SEEIIST), located in Montenegro.

People may think they know about the Western Balkans region because they know its history. However, what people think they know about the Western Balkans is merely one chapter. SEEIIST is part of turning the page.

This international scientific research facility is a great example of where a region once scarred by cross-border conflict is building bridges through science. Creating a place where scientists from all over the world can come to exchange knowledge, ideas and new perspectives. And it's thanks to the vision and determination of the Montenegro Minister for Science, Sanja Damjanović, as well as her counterparts across the region, among others, who ensured the support and the willingness to cooperate through science, and ensure the project came to life.

I am very proud of the European support we have provided to the SEEIIST project over the years through Horizon 2020. With the new geopolitical commission of president-elect Ursula von der Leyen due to take office soon, I am confident that the European Commission will continue to see great value in this type of science diplomacy.

SCIENCE BUSINESS

Search...

Viewpoint: The Western Balkans urgently need research infrastructures

16 Nov 2022 | Viewpoint

Research infrastructures

A research infrastructure to advance the use of heavy ions in cancer therapy is ready to move forward. The EU now needs to put momentum behind the project, as part of a commitment to development of the Western Balkans and to bridge the east-west divide in science

By Sanja Damjanovic



Sanja Damjanovic, former science minister in Montenegro between 2016 and 2020

European Commissioner Carlos Moedas: Strong advocate for SEEIIST.

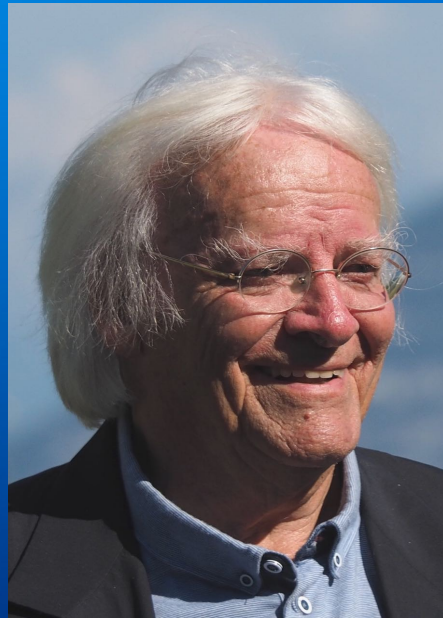
Three ScienceBusiness Articles: Highlighting the significance and potential impact of SEEIIST

**The question arose:
What should SEEIIST be to have
a direct impact on society and
easily attract political support ?**



The proposal for SEEIST to be an **Accelerator-based Research Infrastructure for Cancer Therapy and Biomedical Research with Ion Beams**

came early 2017 from two key pioneers in the use of ion beams to treat cancer:



Prof. Hans J. Specht at Uni HD

- Pioneer of ultra-relativistic heavy ion physics at CERN
- Pioneer of Ion cancer therapy as Scientific Director of GSI Helmholtz Centre for Heavy Ion Research
- He pushed and led the establishment of a pilot project at GSI, where the first 450 patients in Europe were treated with ion-beams from 1997-2008.
- Instrumental in establishing Europe's first hadron cancer therapy clinic, HIT, in Heidelberg



Prof. Ugo Amaldi at CERN

- A pioneer in the design of particle accelerators for cancer treatment, who was instrumental in establishing Europe's second hadron cancer therapy clinic, CNAO, in Pavia, Italy
- President of TERA foundation
- Editor of the Concept Study and pre-TDR for SEEIST

A Pilot Project using ^{12}C ions at GSI, Darmstadt

First patient in Europe treated with Ion-Beams at GSI in 1997



1993-1997 setting up the Pilot project
developing novel technology in 4 y

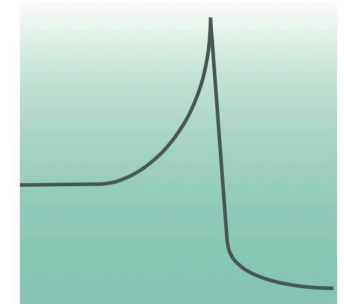
- Rasterscan with intensity modulation
- Treatment plan (Voxelplan + LEM)
- First in-situ PET monitoring for HI
- Fast and safe beam control system
- Hospital-like cave and control room
- Parallel beam operation for physics

1997-2008 Treatment of ~450 Patients
Chordoma, Chondrosarcoma, Prostata...

Inauguration of the Therapy Project at
GSI on 15.09.1998



Construction of a Clinical
Therapy Facility for Cancer
Treatment with Ion Beams




Radiologische Universitätsklinik Heidelberg


Deutsches Krebsforschungszentrum Heidelberg


GSI
Gesellschaft für Schwerionenforschung Darmstadt

Official Project Proposal for Heidelberg
Clinic, handed to the German Gov.
representatives at the inauguration ('98)

Spectacular success, opening the way to the first Ion Clinic in Heidelberg

Technology from GSI to Society

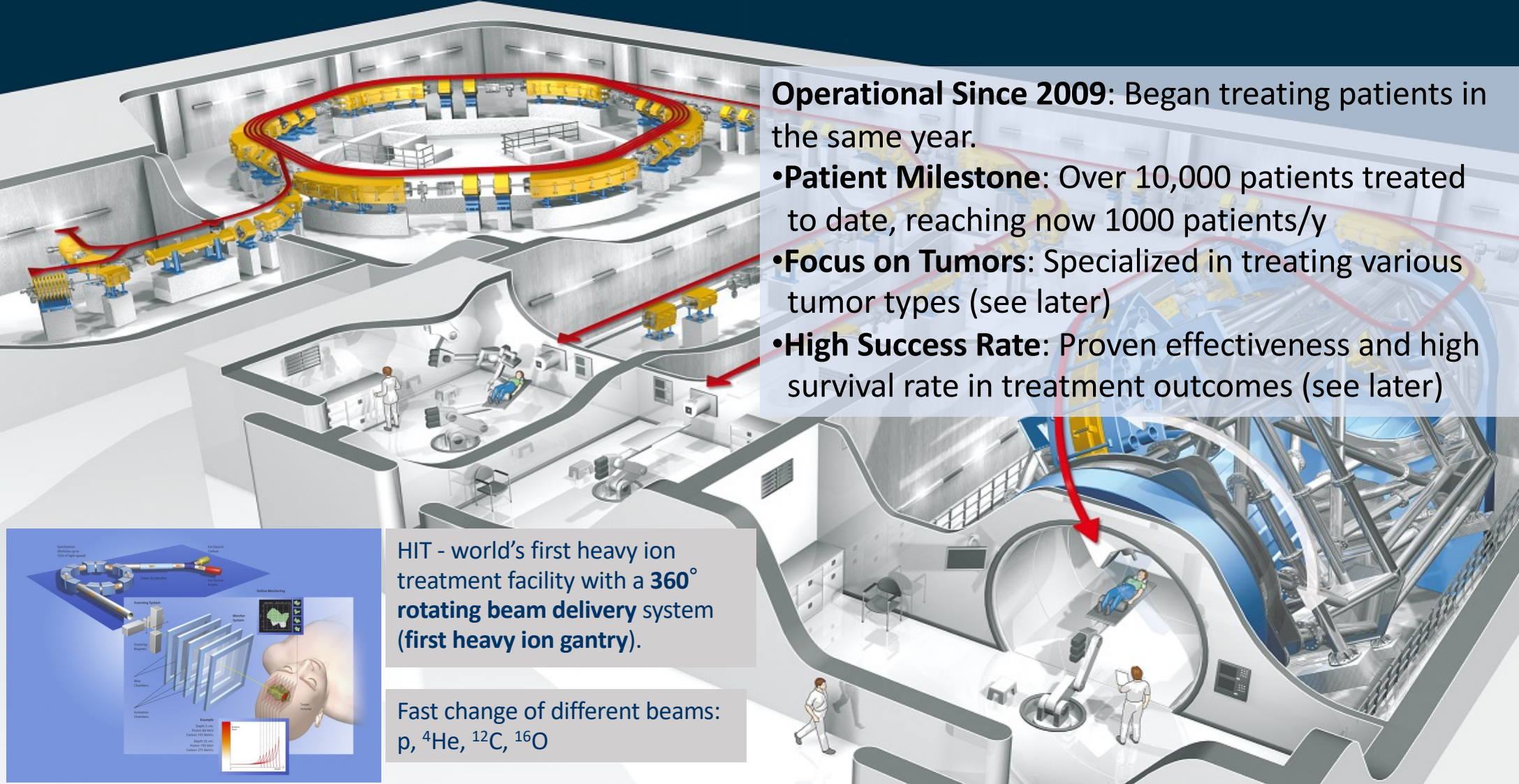


First facility in Europe - Heidelberg Ion Therapy Facility (HIT)



Operational Since 2009: Began treating patients in the same year.

- **Patient Milestone:** Over 10,000 patients treated to date, reaching now 1000 patients/y
- **Focus on Tumors:** Specialized in treating various tumor types (see later)
- **High Success Rate:** Proven effectiveness and high survival rate in treatment outcomes (see later)

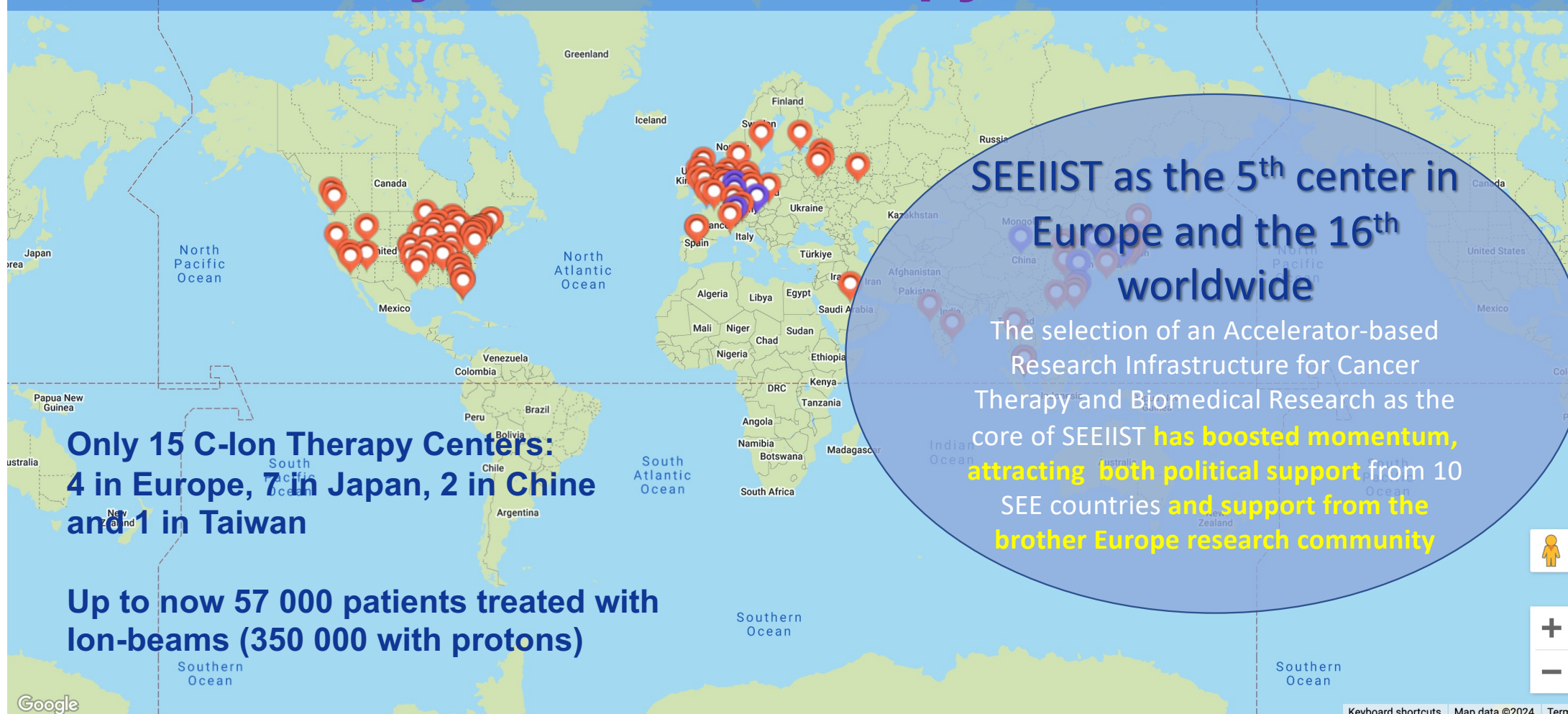


HIT - world's first heavy ion treatment facility with a **360° rotating beam delivery system (first heavy ion gantry)**.

Fast change of different beams:
 p , ^4He , ^{12}C , ^{16}O

Particle Therapy Centers world-wide

only 15 C-Ion Therapy Facilities



Political Milestones – SEEIST goes Regional

As the political lead of SEEIST, appointed by the Government of Montenegro:

- **Role:** Served as a "Science Diplomacy Missionary"
- **2017 Milestone:** As Minister of Science, I visited all SEE countries individually, securing their support for the initiative.

Declaration of Intent signed at CERN on October 25, 2017 by SEE Ministers



Memorandum of Cooperation signed by SEE Prime Ministers at the 6th Summit of the Berlin Process, 2019



In January 2018 first Intergovernmental SEEIST Steering Committee was formed
I was elected to be the first Chair (2018-2021)

Scientific Milestones – SEEIIST attracted support from the broader European Research Community

Fighting against cancer

Develop the next generation of medical accelerators, explore new technologies by leveraging the experience gained from the LHC construction.

Building international cooperation and scientific capacity in South East Europe

Advance European integration, reverse brain drain, connect to Europe

Two Strategic Objectives – One initiative



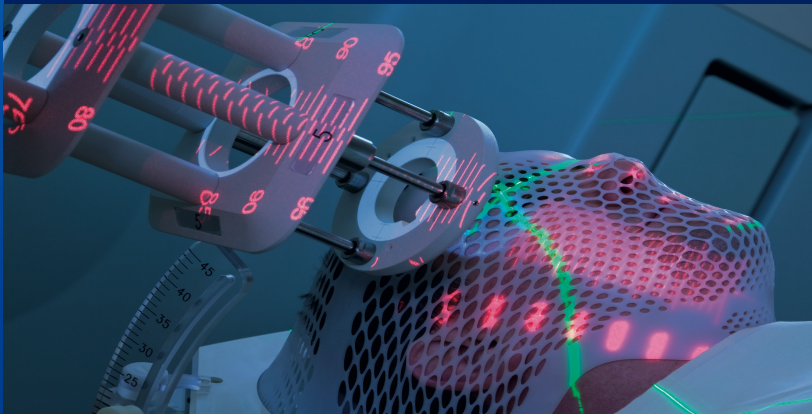
Key Attraction: the Unique Comprehensive Dimension of SEEIIST: both Cancer Therapy and Research Center

SEEIIST: Boosting Pioneering Technology and Research through Global Collaboration



MULTI-DISCIPLINARY RESEARCH WITH HEAVY IONS

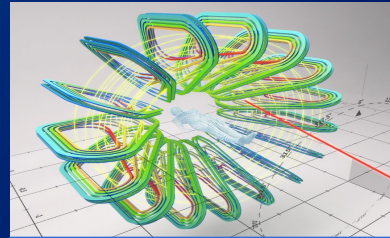
- Pre-clinical (medical, radiobiology)
- Ultra-high dose rates (FLASH therapy)
- Clinical, including clinical trials
- Material research including testing radiation hardness of space microelectronics and shielding material



Cutting-edge innovative and novel research in any of these topics driven by novel technological opportunities

BREAKTHROUGH IN TECHNOLOGY

- Leading-edge multi-turn injection and multiple ion source system (beyond p, C)
- Higher (record) beam intensity (10 times higher)
- Upgraded injector – new high-frequency injector Linac
- Multiple dose delivery modalities reaching unprecedented high dose rates (FLASH treatment tech.)
- Superconducting gantry
- Unique superconducting synchrotron design



With the strong supporting consortium of 18 European research centers and clinics (including CERN and GSI), SEEIIST is driving innovation in medical accelerators and techniques through international collaboration.

Political Milestones – Support by the European Commission

❖ EC – Directorate General for Research and Innovation (EC DG-RTD)

First direct financial support for the SEEST Design Phase

- 1.5 MEUR for the 1st stage of Design Phase (2019)
- Additional 5 MEUR via a competitive Call EU-H2020 INFRAIA – HITRIplus (2021-2025)

SEEST is one of the 6 Leading EU-WB projects in R&I in the Innovation Agenda for the WB



❖ EC - Directorate General for Neighbourhood and Enlargement (DG NEAR)

SEEST became part of the Economic Investment Plan for Western Balkans (part of Global Gateway initiative) as the only Research Infrastructure – 9 billion EUR appointed for the WB 2021-2027



Fight against Cancer

Cancer is the second leading cause of death globally, and was responsible for 10 million deaths in 2020 (WHO)

Globally, nearly 1 in 6 deaths is due to cancer (WHO) – Each year 400 000 children develop cancer

Cancer research declared by the **European Commission** as one of the **five Missions** in the **EU Horizon Europe Programme** - but presently entirely absent from the European RI landscape.

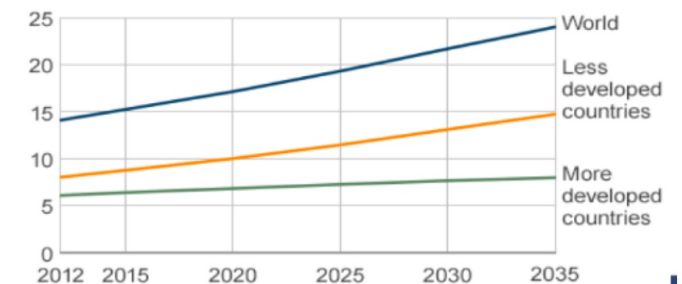
SEEIIST addresses this notable **gap in the European Research Infrastructure landscape**

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012



Predicted Global Cancer Cases

Cases (millions)



Source: WHO GloboCan

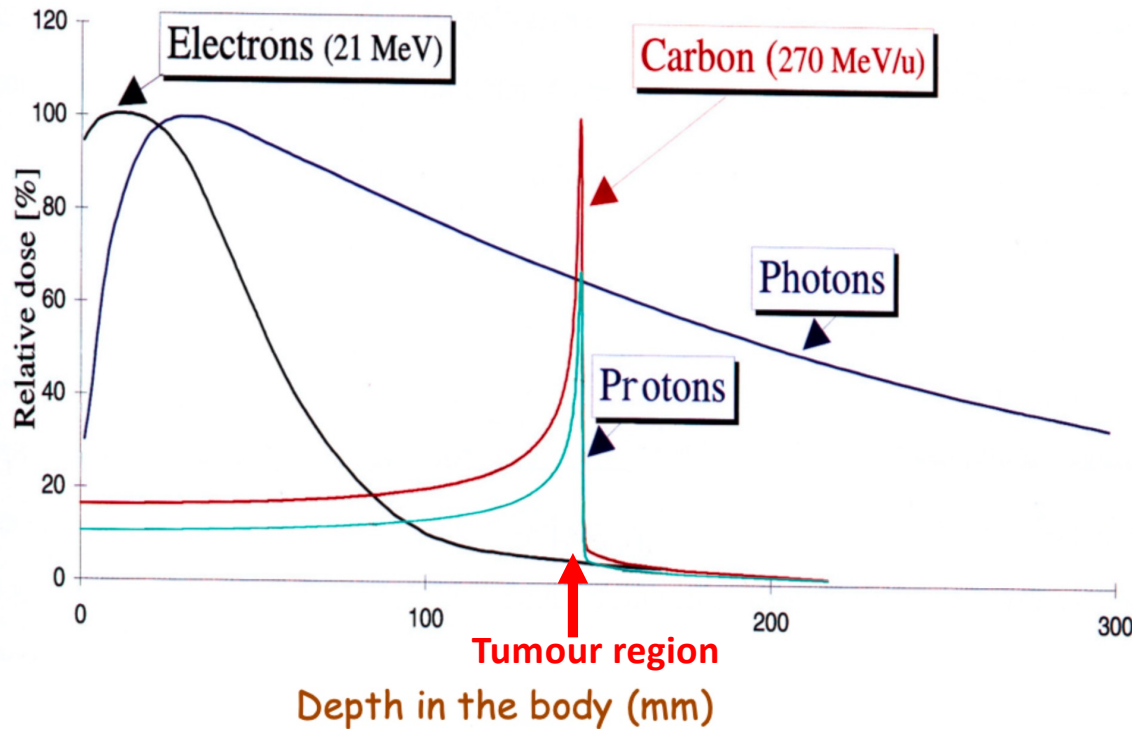
From Conventional to Ion-Beam Radiotherapy



**Why Heavy Charged Particles are
superior to any other radiation in
tumour therapy?**

The beauty of Bragg Peak

Deposited dose along the tissue depth

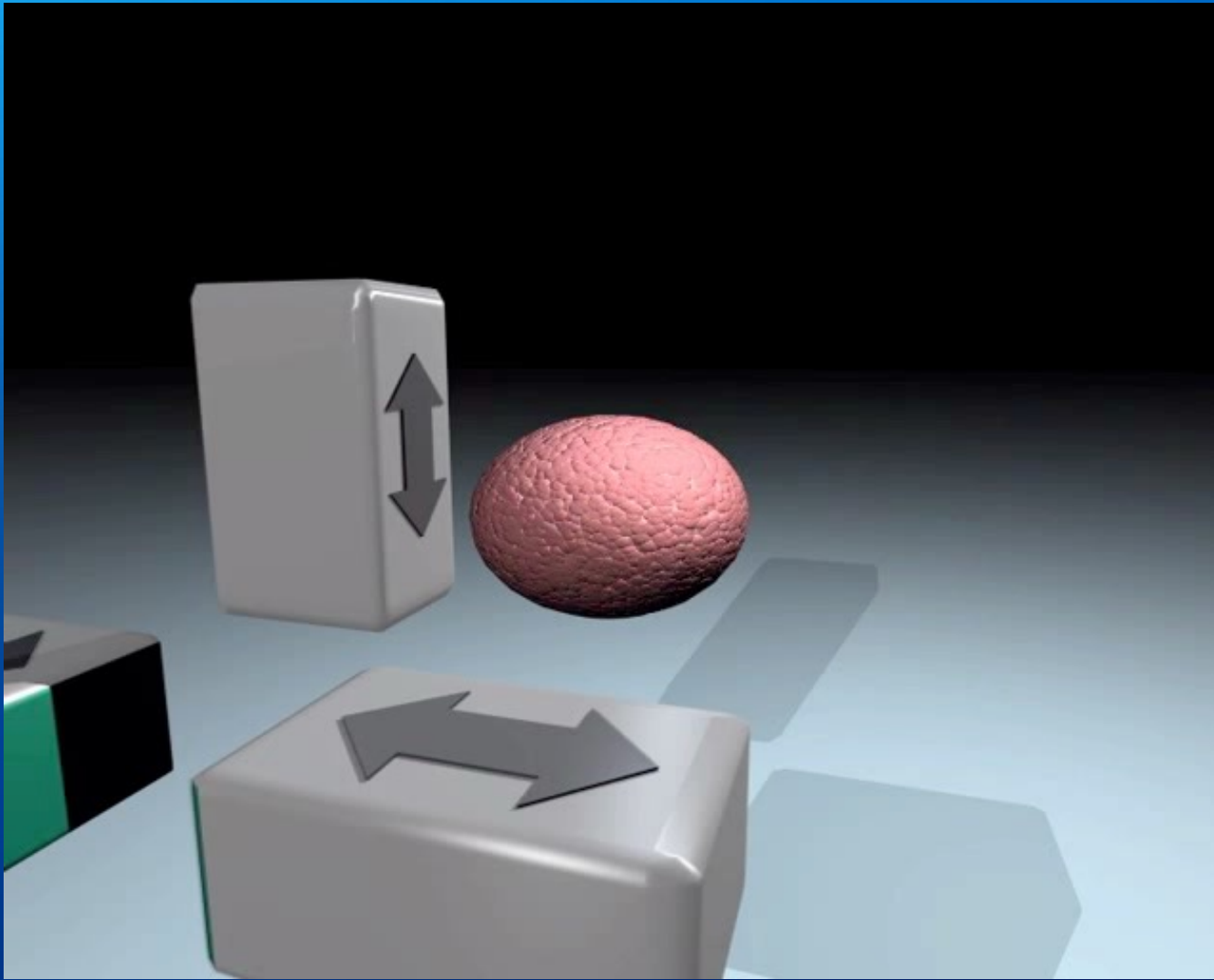


Different from X-rays and Electrons:

- **Heavy charged particles** exhibit minimal lateral and angular scattering.
- These particles travel in virtually straight lines and stop at a specific penetration depth, delivering a **high dose** precisely at the end of the ion path, known as the **Bragg peak**.
- The optimum **dose of heavy ions** can be **precisely localized at the tumour** inside the patient, **protecting surrounding healthy cells**, reaching the tumour wherever it is in the body

Ion therapy is particularly powerful for radioresistant tumours and tumours close to risk organs (C-ions more powerful than protons – much larger effective dose - proportional to Z^2)

Ion Beams scan the Tumour Volume



Ion beams scan the tumour volume of any shape in lines in the same way electrons do in the television tube.

Three-dimensional Irradiation:

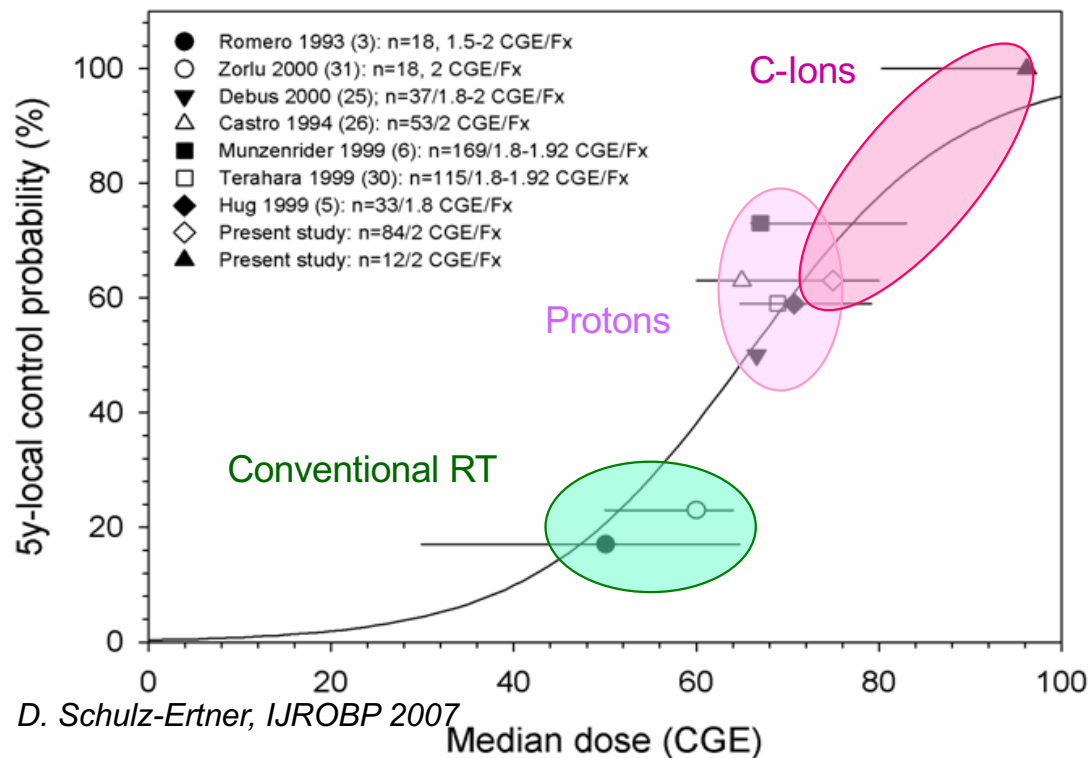
The depth controlled by the energy, while scanning in a plane at a fixed depth - isoenergy slice- achieved by two magnets changing the beam in vertical and horizontal position

Three-dimensional imaging of the irradiated tumour volume with millimeter accuracy – aligning with the precision of the treatment method

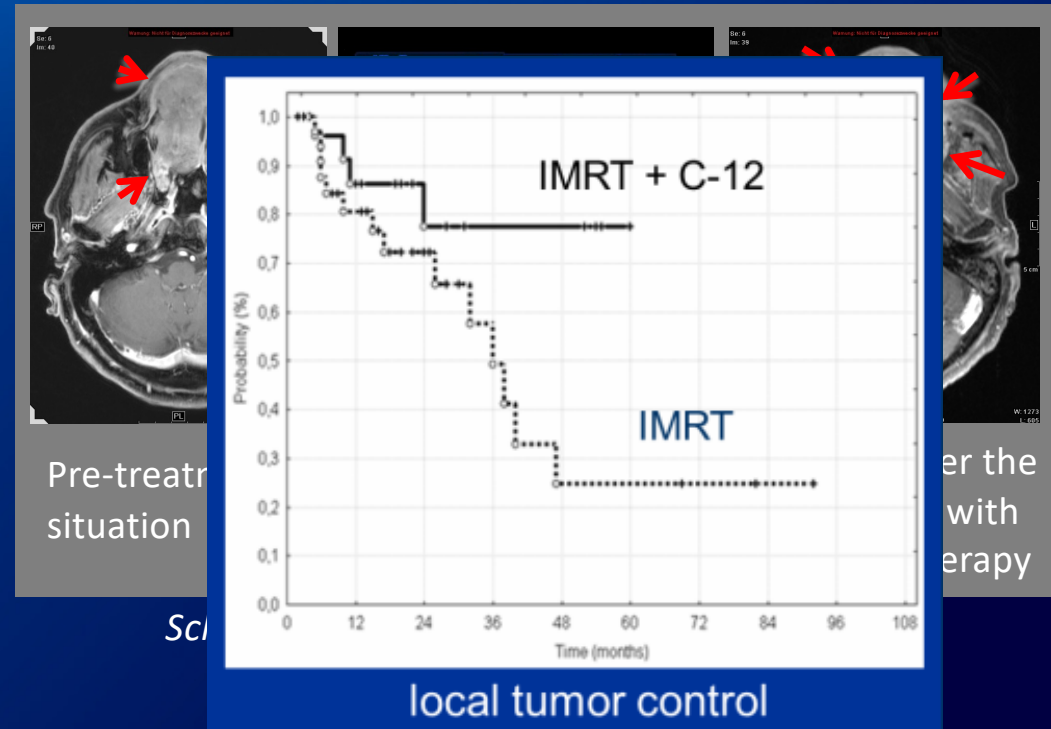
Carbon-ion Therapy - High Effectiveness and Survival Probability

Chordomas of the Skull Base

90% Survival probability 5 years after C-treatment



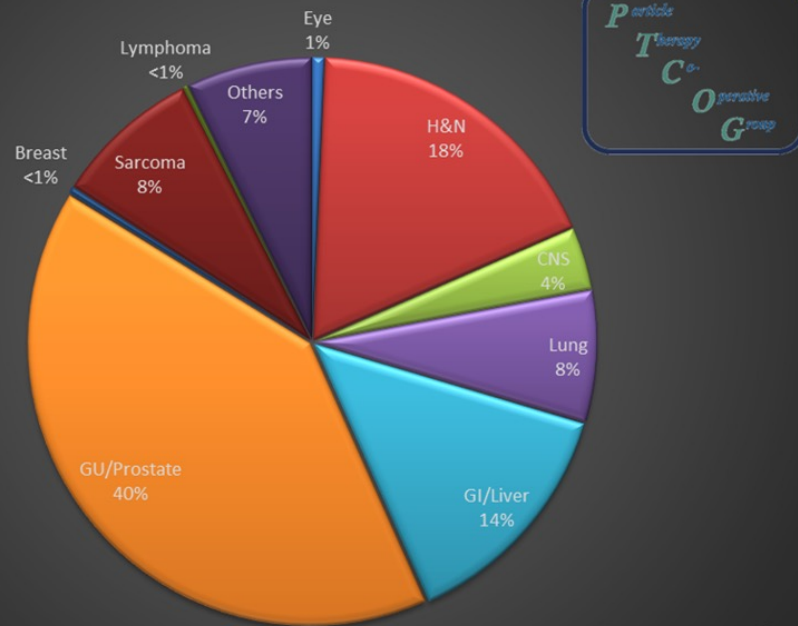
Carbon ion Boost and IMRT highly effective for **Salivary gland tumors**



Cancer Types treated with Ions

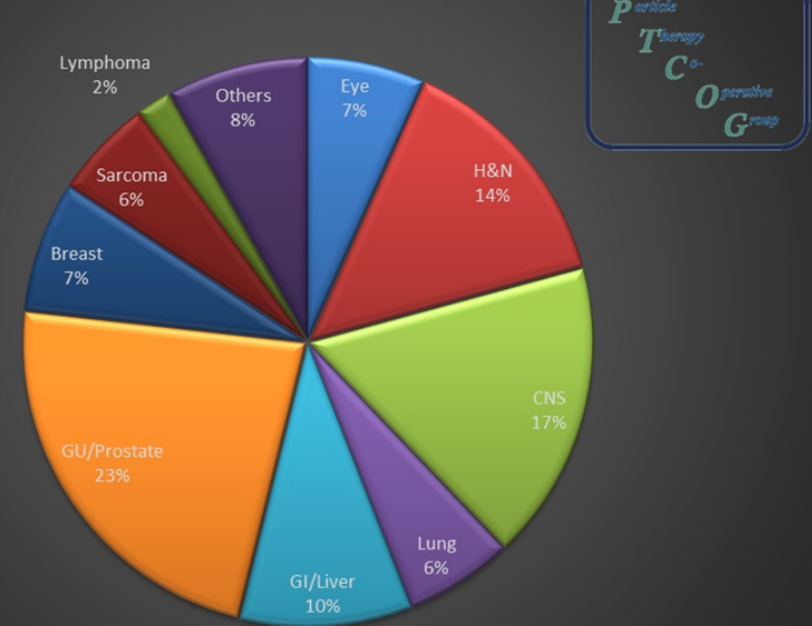


Sites/Indications Treated with C-Ions
Worldwide, 2022



© PTCOG, 2023 /MJ

Sites/Indications Treated with Protons
Worldwide, 2022



© PTCOG, 2023 /MJ

H&N – Head and Neck
CNS – Central Nervous System

Cancer Types treated – more detailed list

Indications currently treated in two German centers (HIT and MIT)

Indications	
Tumors in children and young adults	Ependymoma Retinoblastoma, Medulloblastoma, Glioma, Lymphoma, Sarcoma, Neuroblastoma, Teratoma Craniopharyngeoma
Chordoma and Chondrosarkoma of the skull base	
Cerebral Arteriovenous Malformations (AVM) Mediastinal Lymphoma (protons)	



Source: HIT
Heidelberg

Within phase II clinical trials

Adenoid cystic carcinoma (ACC)

Glioma Grad II/III in adults, glioblastoma

Paraspinal sarcoma and carcinoma, non-operable osteo- and chondrosarcoma of axis skeleton

Meningeoma of skull base - (> 15 ccm) and atypical forms, incompletely resected or sinus cavernosus involvement

Advanced **head and neck tumors** without distant metastases

Hepatocellular carcinoma

Thoracic tumors:

Lung carcinoma (NSCLC, inoperable stage I-III), and pleural mesothelioma stage I-III, if pleuropneumectomy is not possible

Locally advanced **gynecological malignoma**, previously treated with RT or not suitable for brachytherapy.

Esophageal carcinoma not resectable

Soft tissue sarcoma/chordoma am Körperstamm (neo)-adjuvant and primary if inoperable and extremities after extremity conserving surgery

Locally advanced **pancreatic carcinoma** TxNxM0 with (neo)-adjuvant particle therapy or inoperability

Pituitary gland adenoma (inoperable, not suitable for radiosurgery /SRS)

Craniopharyngeoma

Akusticus neurinoma (inoperable, not suitable for radiosurgery /SRS)

Hadron therapy the most powerful, yet still a niche in cancer therapy

Main factors for limiting growing:
Cost and Size

2 MEUR



X-ray linac



Proton single-room



Proton multi-room

250 MEUR



Ion therapy
(protons + carbon ions)

E.g. in 2018 world-wide 22,000 patients were treated with hadron therapy (p,C). In contrast, 25,000,000 patients were treated with conventional radiotherapy

Opportunity to Develop Next-Generation Ion Therapy Facilities to Expand Access to Ion Therapy for a much larger number of patients *by Leveraging Collaboration to advance accelerator technologies and new treatment techniques*

- *More Compact & Cost-Effective, and Higher Performance Designs*
- *Incorporating R&D Innovations like FLASH Therapy*

18 European Research Centers and Clinics across 14 European countries *Leading the development of breakthrough technologies*

SEEIIST as a catalyst – *Strategic partner and Reference User*

Collaborative partners
in the EU H2020
HITRIplus project:

CERN (through NIMMS program), GSI, HIT, CNAO, MedAustron, MIT, Bevatech GmbH, CEA, CIEMAT, COSYLAB, INFN, PSI, Uni Malta, Philipps Uni Marburg, Uppsala Uni, Wigner RC, Technical Uni Riga

CERN Next Ion Medical Machine Study (NIMMS)

+ large number of international partners:

Towards a new generation of accelerator for cancer therapy

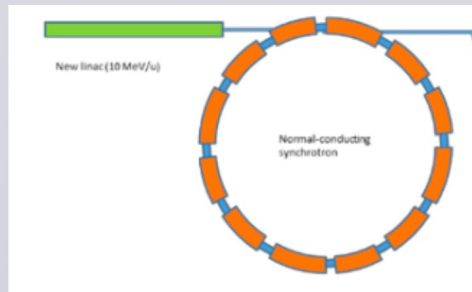
Three alternative accelerator designs

Maurizio Vretenar,
CERN, 19 Oct 2020

Improved synchrotron (warm)

Equipped with several innovative features: multi-turn injection for higher beam intensity, new injector at higher gradient and energy, multiple extraction schemes, multi-ion.

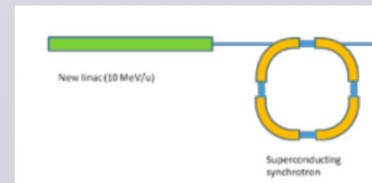
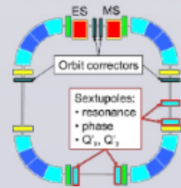
Circumference ~ 75 m



Improved synchrotron (superconducting)

Equipped with the same innovative features as warm, but additionally 90° superconducting magnets.

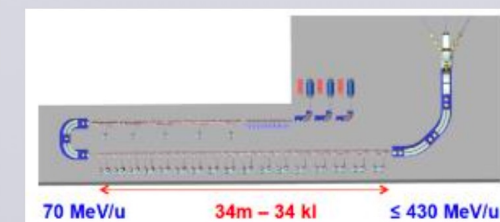
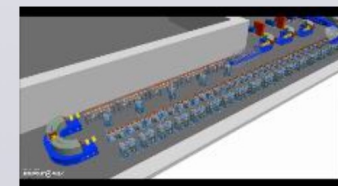
Circumference ~ 27 m



Linear accelerator

Linear sequence of accelerating cells, high pulse frequency.

Length ~ 53 m



GSI Biophysics, alongside international research efforts – Advancing Innovative Flash Radiotherapy - a novel approach using ultra high dose rate

FLASH Therapy with heavy ions – Powerful weapon in the fight against cancer - Killing tumours in less than 1 second with reduced toxicity

With FLASH Therapy – Ultra-High Radiation Dose Delivered in a very short time (Dose Rate of $> 40 \text{ Gy/s}$, delivered time $< 200 \text{ ms}$). For Comparison: Conventional Radiation Dose Rate is 1 Gy/min .

GSI in one of the 10 breakthroughs of 2022: Investigating new weapons in the fight against cancer

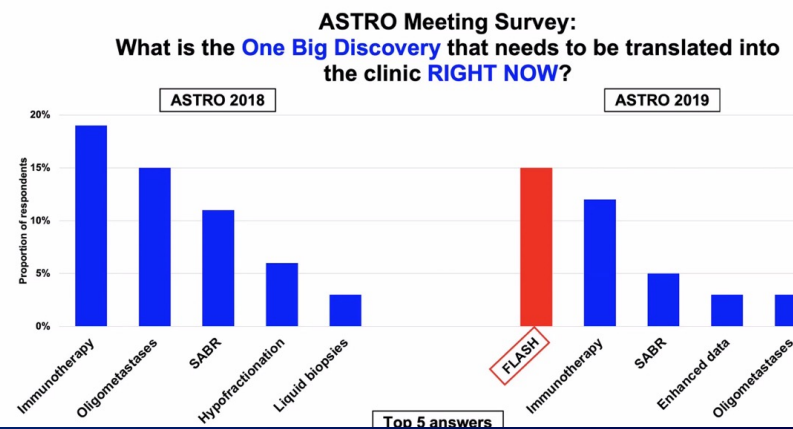
World's leading oncology journal dedicates its cover story to the FLASH method in which GSI has a leading role



19.01.2023 | It could become a powerful weapon in the fight against cancer and open up completely new possibilities for tumor therapy with charged particles. FLASH irradiation – the application of an ultra-high radiation dose in a very short time – is in strong focus worldwide and is being advanced with high expertise at GSI and FAIR. FLASH clinical implementation is one of the top 10 Breakthroughs of the Year 2022 according to "Physics World". In its December issue, the world's

The Hottest Topic in Radiation Oncology!

FLASH „boom“



Marco Durante,
2023, GSI

Timeline for the SEEIST Project

SEEIST is finalising the second, Design Phase, and ready to enter the third, Preparatory Phase



2017-2018:
Concept
Studies

2019:

- Design Study Phase Started

2020/21:

- EU H2020-INFRAIA
- Applied for the ESFRI Roadmap 2021



2025:

Construction
could start

2024:

Ready to start the
Preparatory
Phase

2030:

First patient could be treated



Green concept
for the SEEIST
project

For SEEIST investment of 250.5 MEUR required,
guaranteeing competitiveness in Europe.



**SEEIST
First Green
Particle
Cancer Therapy
and Research**

New Growth Plan for the Western Balkans

Boosting the Western Balkans' socio-economic convergence with the EU & accelerating EU reforms



NOVEMBER 2023

#WesternBalkans
#EUEnlargement

€6 billion
€2 billion in grants
€4 billion in loans



SEE



South East European
International Institute
for Sustainable Technologies

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SEEIIST: A potential Flagship project for EU Enlargement





In Memoriam: Professor Dr. Hans J. Specht (1936-2024)



This presentation is dedicated to the memory of Professor Dr. Hans J. Specht, whose pioneering work in ultra-relativistic heavy-ion physics had a profound impact on society leading to significant advancements in cancer treatment. His rare combination of scientific excellence and strong management, along with his ability to make brave decisions, has left a lasting impact on society.

He was a strong advocate for international cooperation and played a crucial role for development and success of SEEIIST.

BKP

Robert R. Wilson (1914-2000) first realized the potential of using charged particles for cancer therapy

- 1946 Ion therapy for deep seated tumors
- 1954 Lawrence Berkeley Laboratory, USA treated first patient with proton therapy
- 1957 Uppsala starts proton treatment
- 1975 Lawrence Berkeley Laboratory, USA starts using heavy charged particle
- 1990 **The world's first hospital based Proton Therapy Facility in Loma Linda (USA)**
- 1994 Carbon Ion Therapy in Chiba (Japan) introduced for the first time
- 1996 Protonen therapy starts in Villingen/Switzerland
- 1997: Carbon Ion Therapy was introduced for the first time in Europe at GSI, Darmstadt, Germany
- 2009 First Ion Therapy Facility in Europe – Heidelberg Ion Therapy Center (HIT)**
- CNAO, Hyogo, Gunma, MedAustron,...**

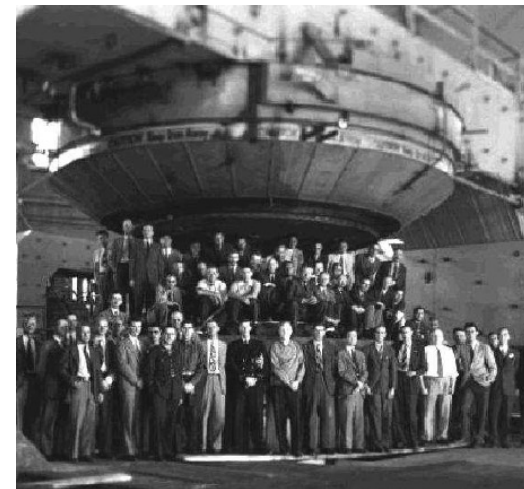
Fundamental
Research

Clinical
Research

Clinical
Application



Robert R. Wilson – first recognition that protons can be used clinically



1954 – Berkeley Lab (USA) treats the first patient With 184 inch Cyclotron

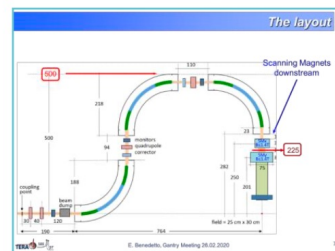
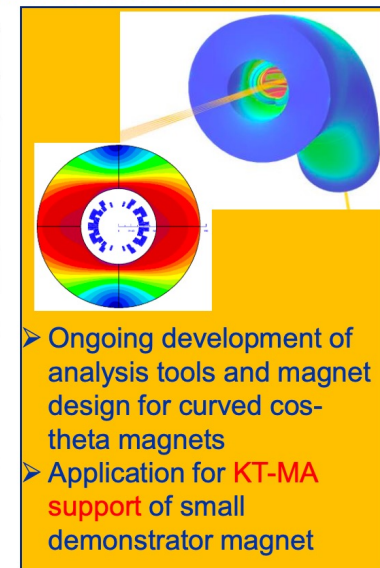
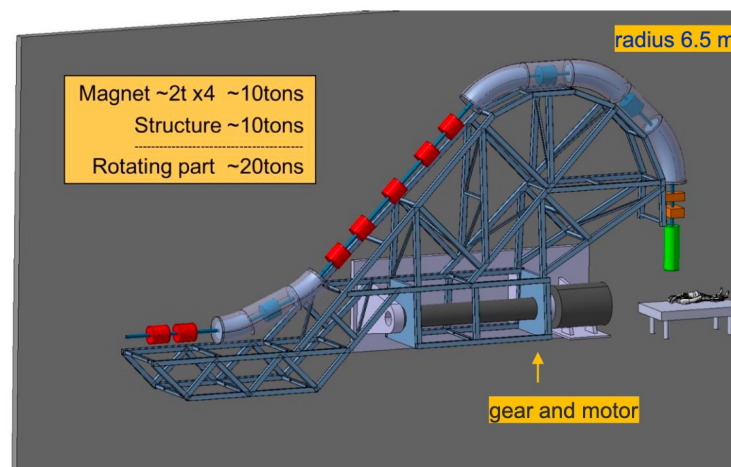
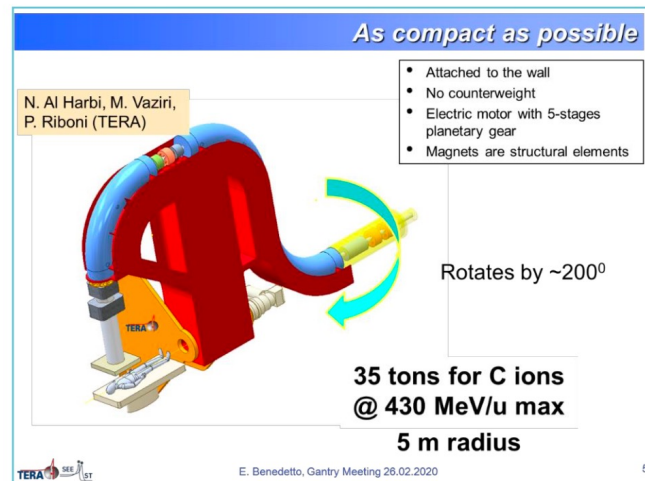
Development of a Superconducting Gantry

Gantry option 1

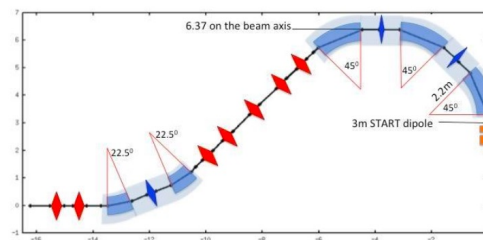
U. Amaldi, N. Al Harbi, P. Riboni (TERA)
L. Gentini, M. Karppinen, D. Perini, D. Tommasini (CERN)
E. Benedetto (TERA/SEEIIST)
M. Pullia (CNAO)

Basic idea from TERA: 5T 90° CCT magnets, light structure attached to a wall, rotating by only 180°

A CERN team is developing a more conservative version, compatible with the CNAO schedule, based on 3T cos-theta magnets at maximum 45°



Small aperture (40mm)
Scanning magnets downstream



Optics completed:

- Bending sections inside 2 cryostats: 45°, 135° with SC quads between dipoles (achromaticity)
 - Warm quadrupoles between cryostats
- Source Axis Distance 2.5 m – challenge for the scanning magnets

FLASH Therapy

- FLASH is very promising for the future of radiation oncology
- Whilst charged particles are the most mature technique for clinical translational, more pre-clinical research is needed
- Following experiments with electrons, photons, and protons, we confirmed for the first time the FLASH effect with high-energy ^{12}C -ions *in vitro* and *in vivo*.
- In addition to the reduction of normal tissue toxicity, we measured reduced tumor growth and distal metastasis. **The suppression of lung metastases, may be a unique feature of particle beams.**
- Beamtime in 2024-2025 at GSI will clarify the role of C-ions in FLASH radiotherapy and the potential for clinical translation

Pascal, treated in the carbon ion pilot project



- Chondrosarcoma discovered and surgically removed in 2003
- Recurring tumor in 2007 at age 8
- Treated in GSI Cave M with carbon ions
- Local control of tumor for 10 years and counting
- Under regular supervision in Heidelberg
- 2017 - preparing to enroll in informatics
- No longterm side effects



<http://www.deutsche-uniklinika.de/themen-die-bewegen/hinter-den-kulissen-patienten-erzaehlen/chondrosarkom/>

PEDIATRIC MEDULLOBLASTOMA

