South East European International Institute for Sustainable Technologies (SEEIIST)

L.Litov

SEEIIST

- Proposed by Herwig Shopper – former director general of CERN
- Objectives of the project
  - ✓ to promote collaboration between science, technology and industry
  - ✓ to provide platforms for the development of the education
  - ✓ technology transfer from European laboratories like CERN and others
  - ✓ mitigate tensions between countries in the region
  - ✓ to form a research nucleus in the region of South-East Europe
- The goals can only be achieved with one major new Institute based on the latest technologies to enable 'first class research'

- Participants
- Albania,
- Bosnia and Herzegovina,
- Bulgaria,
- Greece,
- Montenegro,
- Republic of Croatia,
- Republic of Kosovo,
- Republic of Nord Macedonia,
- Republic of Slovenia,
- Republic of Serbia

Political steps

Declaration of Intent signed at CERN on October 25, 2017

Signature of Declaration of Intent by SEE Ministers of Science/corresponding Ministers or their representatives at CERN

DoI – signed by 8 countries
Croatia – ad referendum
Greece – Observer,
signed 2021

Political steps

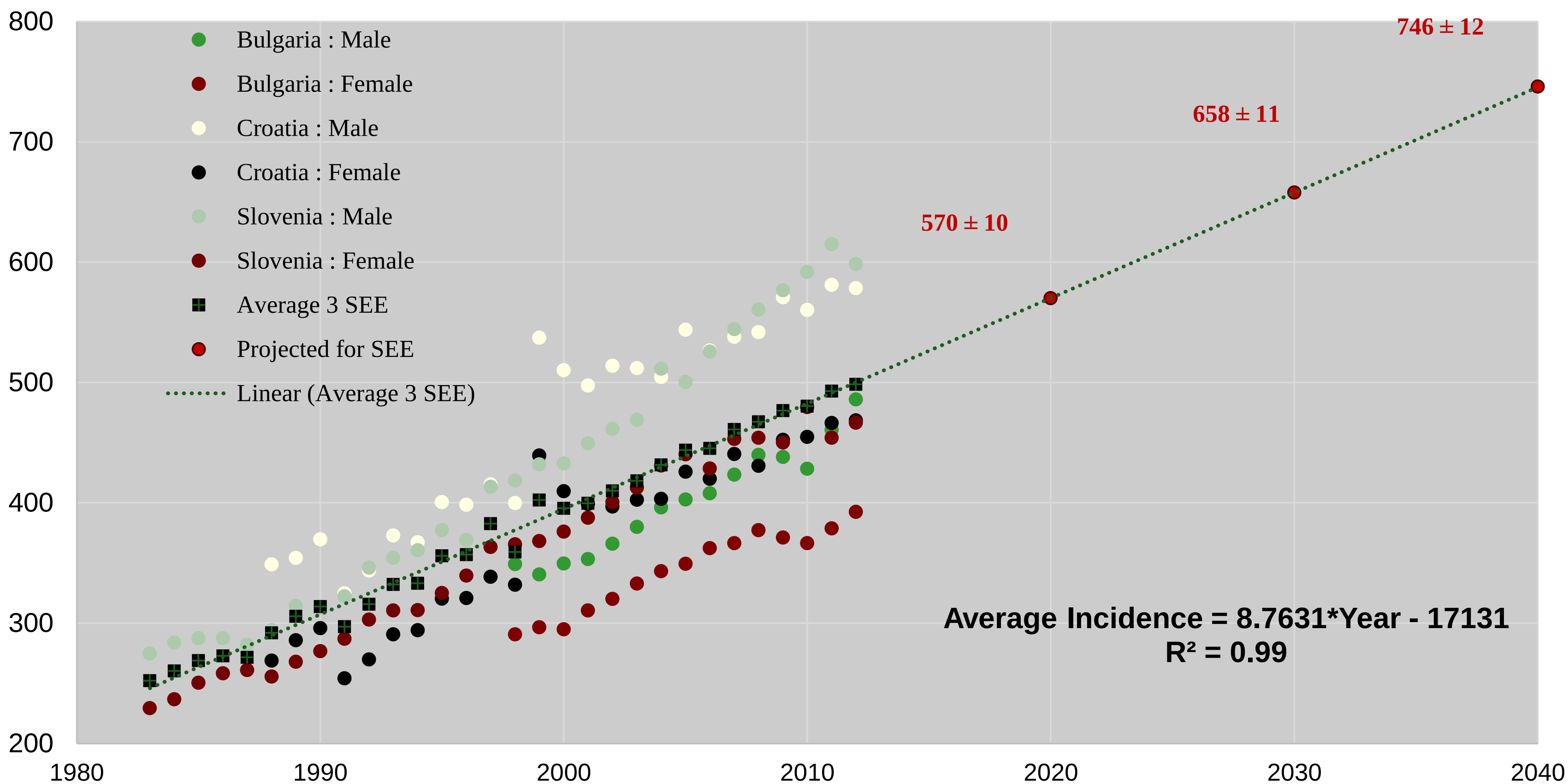
Memorandum of Cooperation signed by six Prime Ministers of the SEE Region

the 6th Summit of the Berlin Process

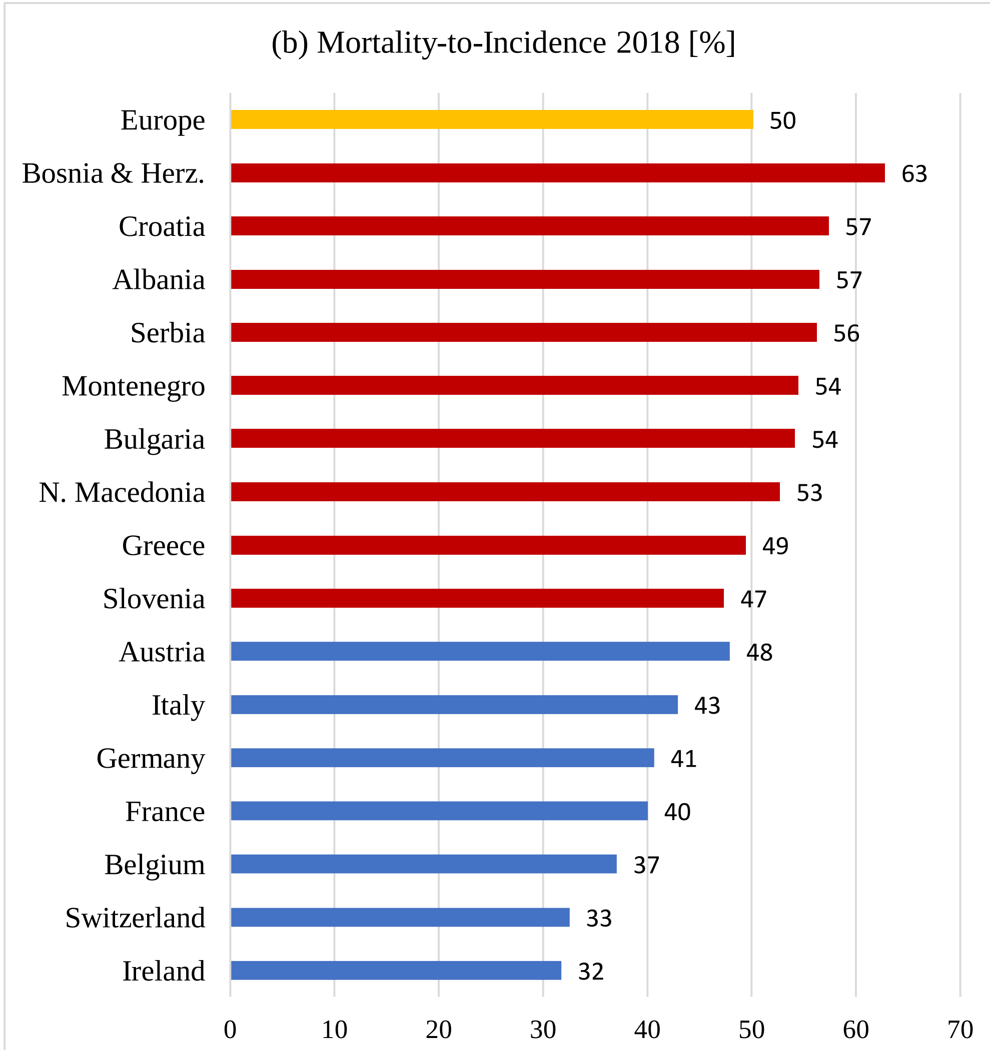
Some arguments for HT

Growing trend of cancer incidence in 100.000 pop

(b) Combined 3 SEE Country Incidence Crude Rates: all cancers (except NMSC, all ages, Females and Males (NS)

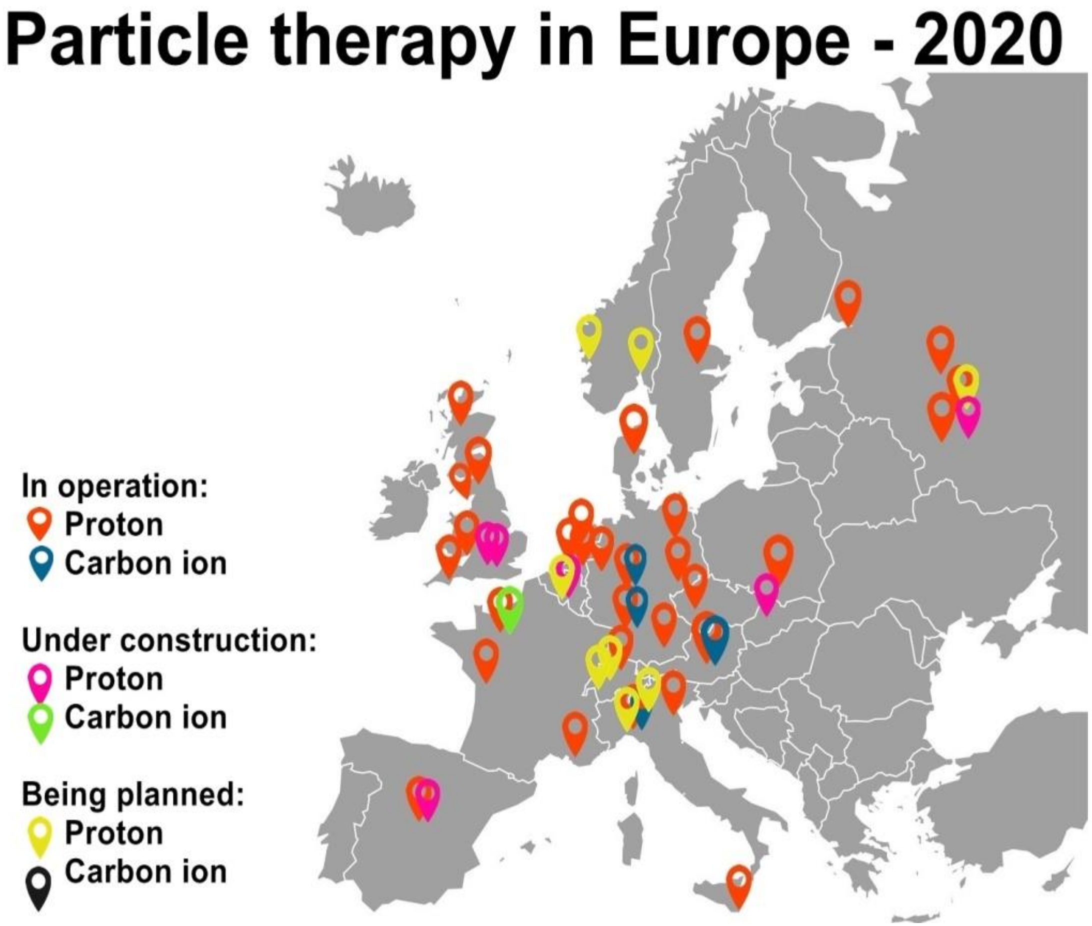


Cancer Statistics – mortality ratio



Some additional arguments for HT

Practically unavailable for the citizens of the region

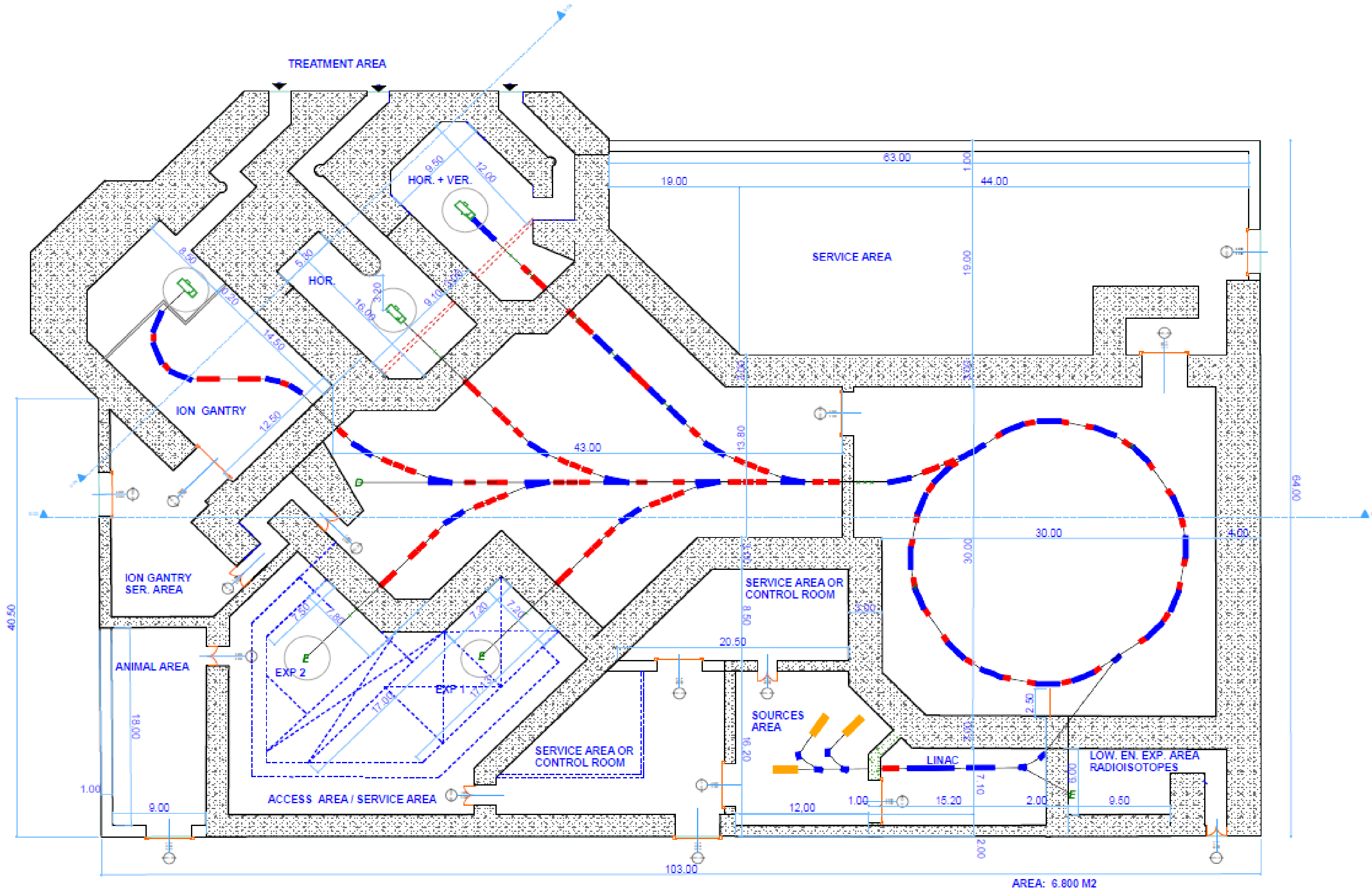


Very expensive – 50 000 Euro at HIT

Expected number of patients

- The population of the 10 countries in the project – 43 million
- Population of Balkan peninsula (including European part of Turkey) – 75 millions
- Estimated number of expected patients
  - ✓ SEEIIST member states > 1400
  - ✓ Balkans > 2450
- Numbers strongly depend from the national protocols for cancer treatment and can vary significantly
  - ✓ The above numbers should be considered as a lower limit
- The SEEIIST HT center will not cover the needs of the region

SEEIIST accelerator complex



Medical parameters

Beams	p, He_2^+, Li_3^+, Be_4^+, B_5^+, C_6^+ (O_8^+)
Beam range	from 3 g/cm^2 to 27 g/cm^2
Bragg peak modulation steps	0.1 g/cm^2
Adjustment accuracy	$\leq \pm 0.025$ g/cm^2
Average dose rate	2 Gy/min (for a volume of 1000 cm^3)
Dose delivery precision	$\leq \pm 2.5\%$
Beam size	4 to 10mm FWHM
Beam size step	1mm
Beam size accuracy	$\leq \pm 0.2$mm
Beam position step	0.1mm
Beam position accuracy	$\leq \pm 0.05$mm
Field size	2×2 cm^2 to 20×20 cm^2 (for H and V fixed beams)

accelerator parameters

Beam particle species	p, He2+, Li3+, Be4+, B5+, C6+, O8+
Energy range	60–250MeV for protons 120–450MeV/u for carbon ions
Energy step	0.02MeV
Relative momentum step p/pmax	1.7×10^{-5}
Beam size	4 to 10mm FWHM for each direction
Beam size step	1mm
Beam position step	0.1mm
Beam position accuracy	≤ ±0.05mm
Max. number of particles per spill at the patient	10^{10} for protons 4×10^{8} for carbon ions
Min. number of particles per spill	10^{8} for protons 4×10^{6} for carbon ions
Nominal number of spills and treatment time	60 spills in 2–3min

SEEIIST


SEE
ST
South East European
International Institute
for Sustainable Technologies

SEEIIST

Center for ion therapy and biomedical research

- Sustainable running of the centre
  - ✓ First requirement is to prove that the centre will run and be used in the most efficient way
- In case we build HT centre with three treatment rooms
  - ✓ 50% acc. time – patient treatment
  - ✓ 50% – research program

Nominal treatment capacity of the Centre		Exploitation level till break-even point	
Number of rooms	3		
Days of operation/year	250		
Treatment hours/day (7 – 14)	5		
Time for fraction	30 min	Capacity reached	70%
Room utilization	95 %	Average number of fractions/patient	18
Room availability	95 %	Number of patients/year	260
Maximal number of fractions/year	6670	**Number of patients/year**	**375**

SEEIIST cost

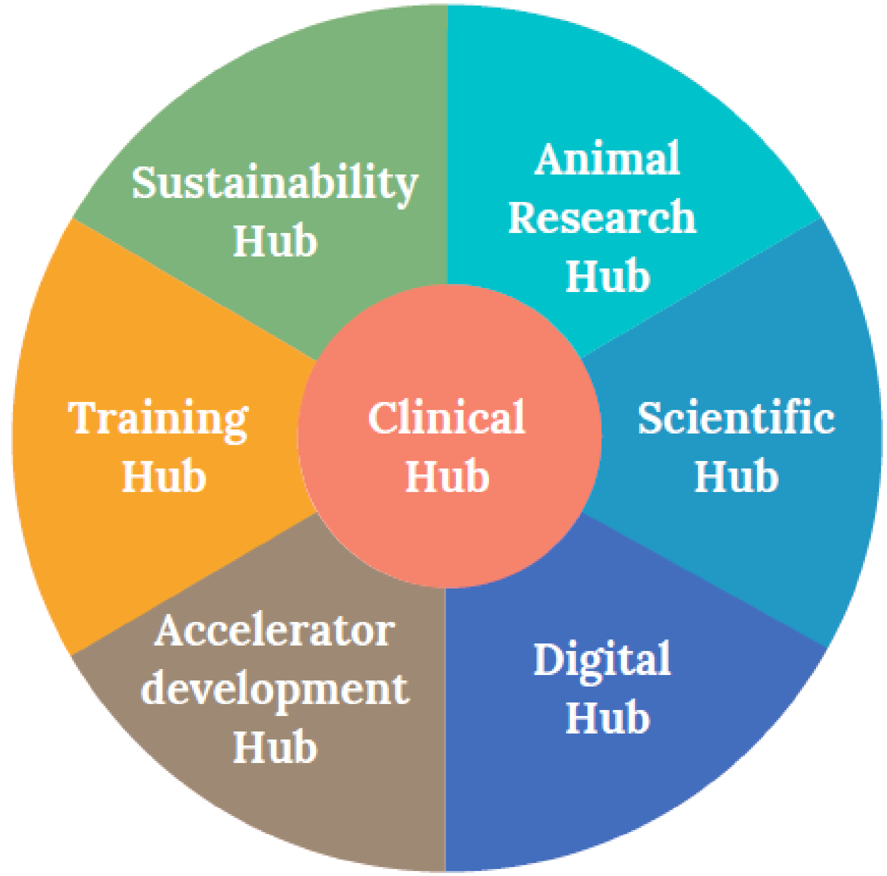
	kEUR
General expenses during construction and commissioning (5.5 years)	16 850
1. Accelerator system	99 600
2. Instrumentation for research	5 150
3. Systems to treat patients with horizontal/vertical beams	27 900
4. Total for carbon-ion gantry	23 500
5. Total for high-tech components	156 150
6. W/C needed during the exploitation phase	4 094
6. Building	45 000
7. Imaging centre	8 000
8. Contingency	22 500
TOTAL	**252 594**

Running cost full operation

Scenario 3: Loan to equity 0%/100%	
Running costs full operation (Milion Euro)	
Investment in research programmes	1,60
Cosumables for treating patients	0,50
Maintenance and upgrade	4,80
Power and utilities	2,00
Personnel	7,70
General expenses	1,50
Expenses on imaging activity	0,22
Total	**18,32**
Investment costs per year (for 30 years)	**0,00**
Income due to the treatment of 375 patients at unit fee of 25.000	-9,38
Income from imaging activity	-0,70
Net Sum of Membership fee	**8,25**

Hubs and Networks

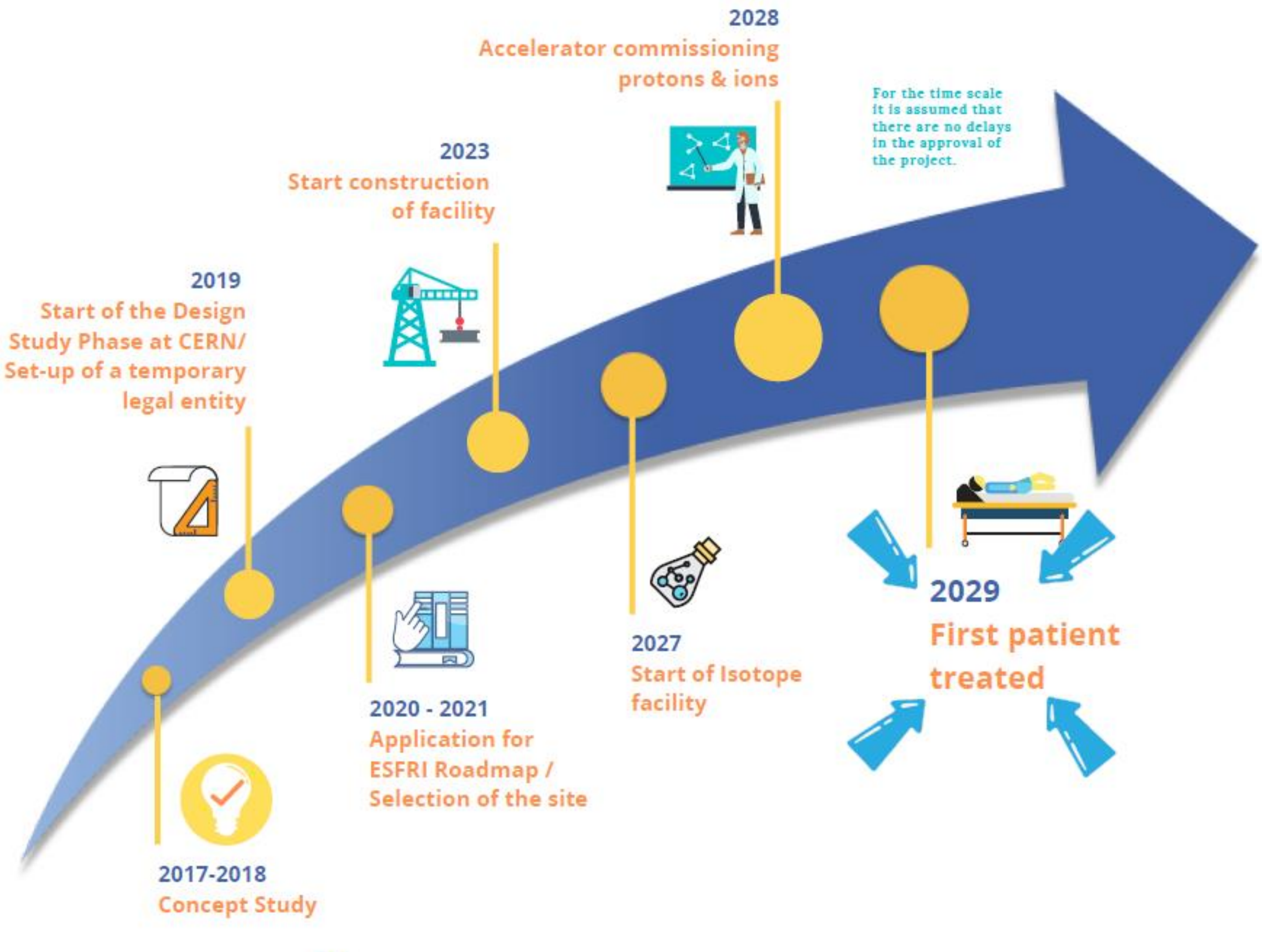
- Distributed infrastructure
  - Digital Hub
  - Accelerator development Hub
  - Scientific Hub (Radiobiology)
  - Sustainability Hub (Sun Power)
  - Training Hub
  - Animal Research Hub
  - Imaging Hub
- WG – Hubs and Networks
- Hubs can be established earlier than central infrastructure



Stages of the project

- Stages of the project
- Preparatory phase
  - First stage
    - preparation of Conceptual Design (CDR)
  - Second stage –
    - detailed technical design of the infrastructure (TDR)
    - Legal framework and establishment of the Institute
    - Business plan
- Construction phase – 5-6 years
- Running
- Detailed work plan with corresponding time scale was developed

Time scale


2028
Accelerator commissioning protons & ions
For the time scale it is assumed that there are no delays in the approval of the project.
2023
Start construction of facility
2019
Start of the Design Study Phase at CERN/ Set-up of a temporary legal entity
2029
First patient treated
2027
Start of Isotope facility
2020 - 2021
Application for ESFRI Roadmap / Selection of the site
2017-2018
Concept Study

Research Program

- ❑ Science community
  - ✓ Supported by CERN and GSI
  - ✓ SEEIIST is embedded in
    - European Network for Light Ion Therapy (ENLIGHT)
    - Infrastructure in Proton International Research (INSPIRE), Manchester Univ.
    - European Particle Therapy Network (EPTN) – task force of European Society for Radiotherapy and Oncology
    - International Biophysics Collaboration (IBC) – at FAIR
  - ✓ HITRIplus
  - ✓ Collaboration agreements with CERN, PSI, CNAO, ICTP

Research Program

- Research is main mission of SEEIIST
  - ✓ Two very large experimental halls
  - ✓ High duty cycle linear accelerator (7 MeV/u) – radioisotopes
  - ✓ Irradiation of small and large animals
  - ✓ Most advanced accelerator technology
    - ➢ Dose delivery in single synchrotron cycle
    - ➢ Fast extraction and shaping of the beam – FLASH therapy
  - ✓ Large number of scientific and technical staff to support research activities of the external teams
  - ✓ At least 50% of the days + nights and weekends will be used for non-clinical research

Research Program

❑ Research program

- ✓ Patients will be enrolled in clinical trials
- ✓ New protocols and methods for cancer treatment
- ✓ Combined radio and immunotherapy
- ✓ Radiation genetics
- ✓ Preclinical in-vitro and in-vivo radiobilogy
- ✓ Medical physics (beams, dose control, imaging etc.)
- ✓ New materials
- ✓ Isotopes for imaging and cancer treatment

Current status

- Preparatory phase
  - preparation of Conceptual Design (CDR) – in process of completion
  - detailed technical design of the infrastructure (TDR)
  - Accelerator design – ongoing (HITRI+)
  - Gentry design – ongoing (HITRI+)
  - Legal framework and establishment of the Institute – ready
  - Business plan – ready (to be updated due to inflation)
  - Site selection procedure and requirements

Thank you for your attention!

SEEIIST Association

- The SC decided to establish the Association at its 5th Meeting, held on 27 June 2019 in Sarajevo, Bosnia and Herzegovina
- A temporary solution for legal entity
- Established on 8 August 2019 under Swiss low
- Seat is located in Geneva, Switzerland
- Purpose
  - In the public interest, to promote, encourage and support the interests of the South East European International Institute for Sustainable Technologies (SEEIIST)
- The Association is a not-for-profit organization
- Resources
  - grants;
  - private and public subsidies;
  - any other resources authorized by the law

SEEIIST Association

- CERN
  - Framework Collaboration agreement KN 4962
  - Development of next generation ion therapy accelerators and associated systems
- HITRI+ - Heavy Ion Therapy Research Integration plus
  - HORIZON 2020
  - Coordinated by CNAO
  - 18 participating organizations
  - Contract is signed by the EC
- Collaboration agreements with CNAO, ICTP

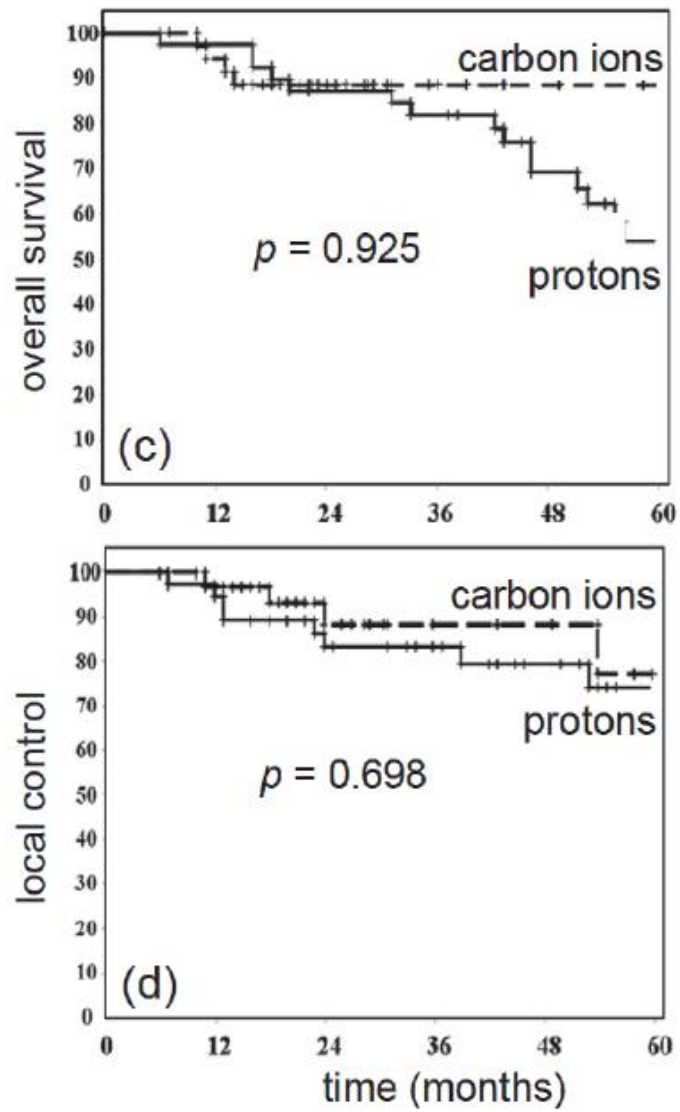
Association agreements

- Ministry of Science of Montenegro - Agreement for Cooperation on establishment of the SEEIIST
  - Further development of the SEEIIST project
  - Applications for funds from EC (H 2020, HORIZON Europe 2021 etc.)
  - Participation in the activities in the field of Science diplomacy
  - Building human capacity for the future Institute
  - Organization of the work of the SEEIIST bodies
- DLR - EC
  - Service contract - Advancing the Design of the SEEIIST
  - Initially three subcontractors – CERN, GSI, SEA
  - Amendment 2 – SEEIIST Association
  - Amendment 3 - SEEIIST Association

Medical program and clinical research

- Protons and ions (C)
- Clinical trials comparing protons and C-ions

  - Adenoid cystic carcinoma of the head and neck region



Medical program and clinical research

❑ Ongoing clinical trials

Brief title	ID Status (patients)	Sponsors	Phase	Condition	Arm 1	Arm 2
C-ion radiotherapy for glioblastoma	NCT01165671 CLEOPATRA Completed (??)	Heidelberg University, Germany	II	Primary glioblastoma	Protons*,$	C-ions*,$
Carbon ion radiotherapy for recurrent gliomas	NCT01166308 CINDERELLA Completed (436)	Heidelberg University, Germany	II	High grade glioma	X-rays£	C-ions
Trial of proton versus carbon ion radiation therapy in patients with chondrosarcoma	NCT01182753 CSP12C Recruiting (154)	Heidelberg University, Germany	III	Low and inter-mediate grade skull base chondrosarco ma	Protons	C-ions
Randomized trial of proton vs. carbon ion radiation therapy in patients with chordoma	NCT01182779 Recruiting (319)	Heidelberg University, Germany	III	Chordoma of the skull base	Protons	C-ions
Ion prostate irradiation	NCT01641185 IPI Completed (??)	Heidelberg University, Germany	II	Prostate cancer	Protons	C-ions
Comparison of proton and carbon ion radiotherapy with advanced photon radiotherapy in skull base meningiomas	NCT01795300 PINOCCHIO Not yet recruiting (80)	Heidelberg University, Germany	III	Skull base meningioma	X-ray *vs* Protons *vs*	C-ions

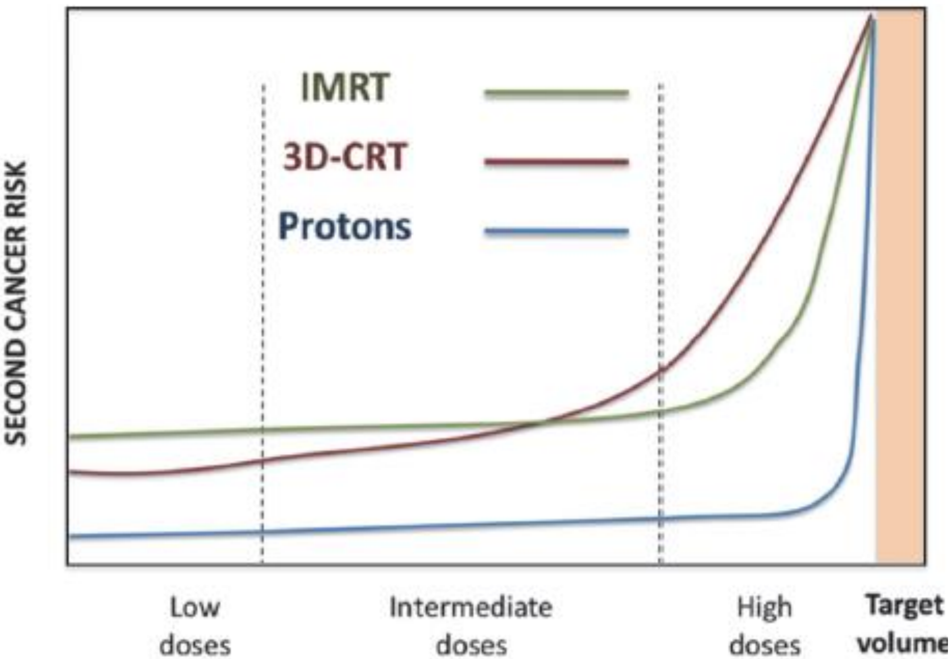
Medical program and clinical research

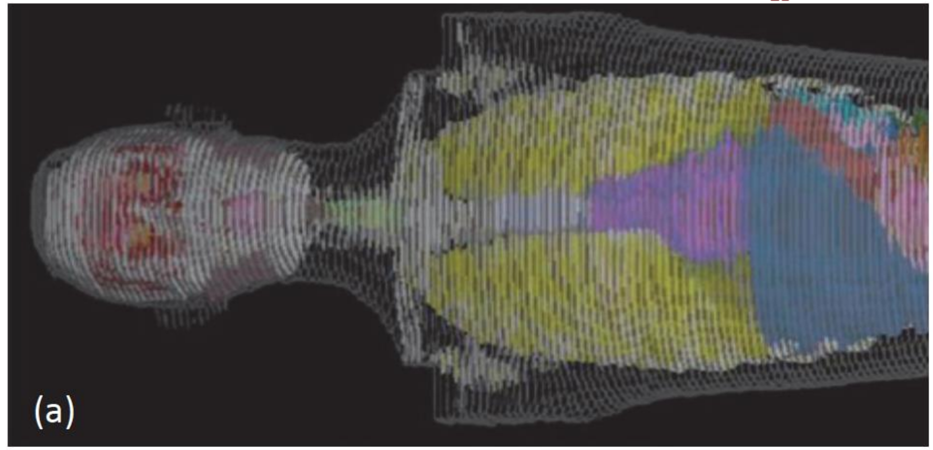
❑ Ongoing clinical trials

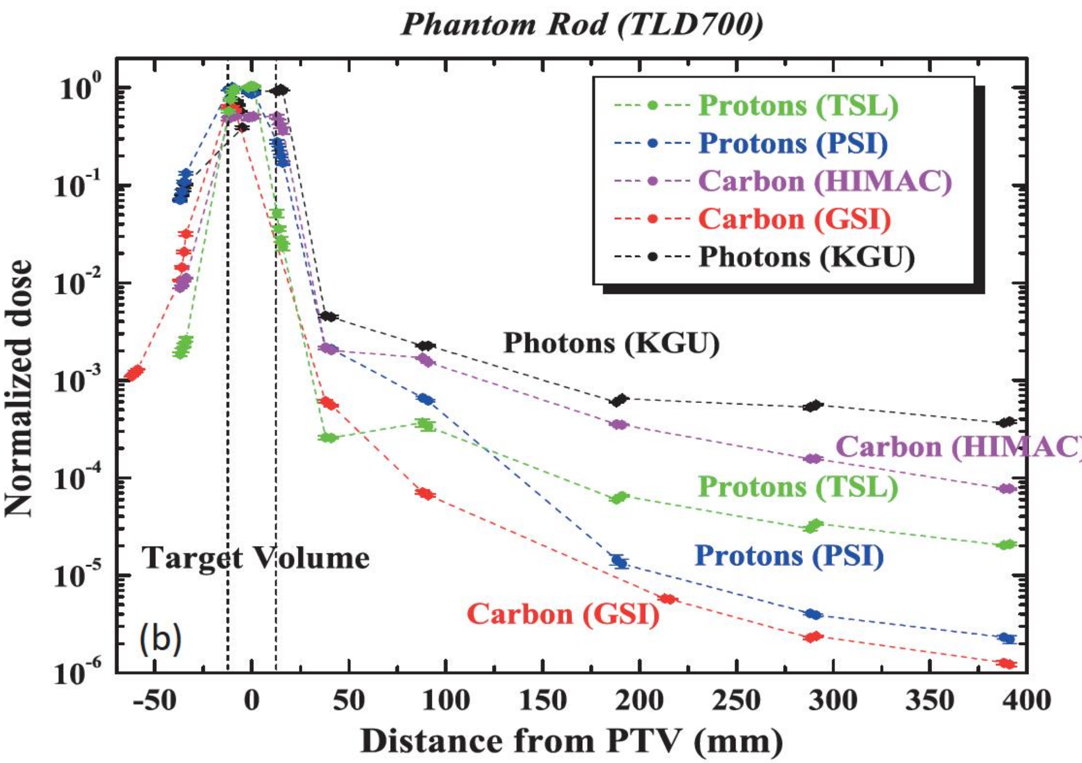
Ion prostate irradiation	NCT01641185 IPI Completed (??)	Heidelberg University, Germany	II	Prostate cancer	Protons	C-ions
Comparison of proton and carbon ion radiotherapy with advanced photon radiotherapy in skull base meningiomas	NCT01795300 PINOCCHIO Not yet recruiting (80)	Heidelberg University, Germany	III	Skull base meningioma	X-ray *vs* Protons *vs*	C-ions
Ion irradiation of sacrococcygeal chordoma	NCT01811394 ISAC Recruiting (100)	Heidelberg University, Germany	II	Sacrococcygeal chordoma	Protons	C-ions
Randomized C-ions vs. IMRT for radioresistant tumors	NCT02838602 ETOILE Recruiting (250)	Lyon University Hospitals, France	III	Adenoid cystic carcinoma, chordoma and sarcomas	IMRT or protons in France	C-ions at CNAO in Italy
Sacral chordoma: surgery versus definitive radiation therapy in primary localized disease	NCT02986516 SACRO (100)	European multicentric, Italian sarcoma group	III	Sacral chordomas	Surgery	C-ions, Protons or mix Rx-P
Prospective multicenter randomized trial of carbon ion vs. conventional radiotherapy for pancreas cancer	NCT03536182 CIPHER Not yet recruiting	Toshiba and UT South-western, Dallas, TX	III	Locally advanced pancreatic cancer	X-rays*	C-ions*
Carbon ion re-radiotherapy in patients with recurrent or progressive locally advanced headand-neck cancer	NCT04185974 CARE Not yet recruiting	Heidelberg University, Germany	II	Recurrent H&N cancers	X-rays	C-ions
Neoadjuvant irradiation of retroperitoneal soft tissue sarcoma with ions	NCT04219202 Retro-Ion Recruiting	Heidelberg University, Germany	II	Retroperitoneal soft tissue sarcoma	Protons	C-ions
Prospective trial comparing carbon ions to IMRT in pancreatic cancer	BAA-N01CM51007- 51 Not yet recruiting	NCI, USA	I/III	Locally advanced pancreatic cancer	X-rays*	C-ions*

Medical program and clinical research

- Pediatric patients







Medical program

- Types of tumors to be treated and their epidemiology
- Highest priority protons and ions

Types of tumour eligible with highest priority for proton therapy	Types of tumours elegible with highest priority for ion therapy (carbon)
Adults' skull base tumours. Adults' unresectable or relapsing meningioma. Other rare adults' central nervous system tumours. Childs' central nervous system tumours. Any other child's solid tumours.	Adenoidcysiic carcinomas of salivary glans, including head&neck and thorax, sinus adenocarcinomas Mucinous melanomas of head and neck, chordomas and chondrosarcomas of skull base and spine. Soft tissues sarcomas of low and medium grade, unresectable or partially resectable without threatening metastasis. Non-small cell lung carcinomas, of small and medium size (N0, M0) unsuitable for surgery. Pelvic local relapses of adenocarcinomas, M0 and previously irradiated by X-rays. Hepatocarcinomas unique and of large size
Total: about 80 cases/year for 10 million inhabitants	**Total: about 200 cases/year for 10 million inhabitants**

Medical program

- Types of tumors to be treated and their epidemiology
- Indications of secondary priority for light ions therapy

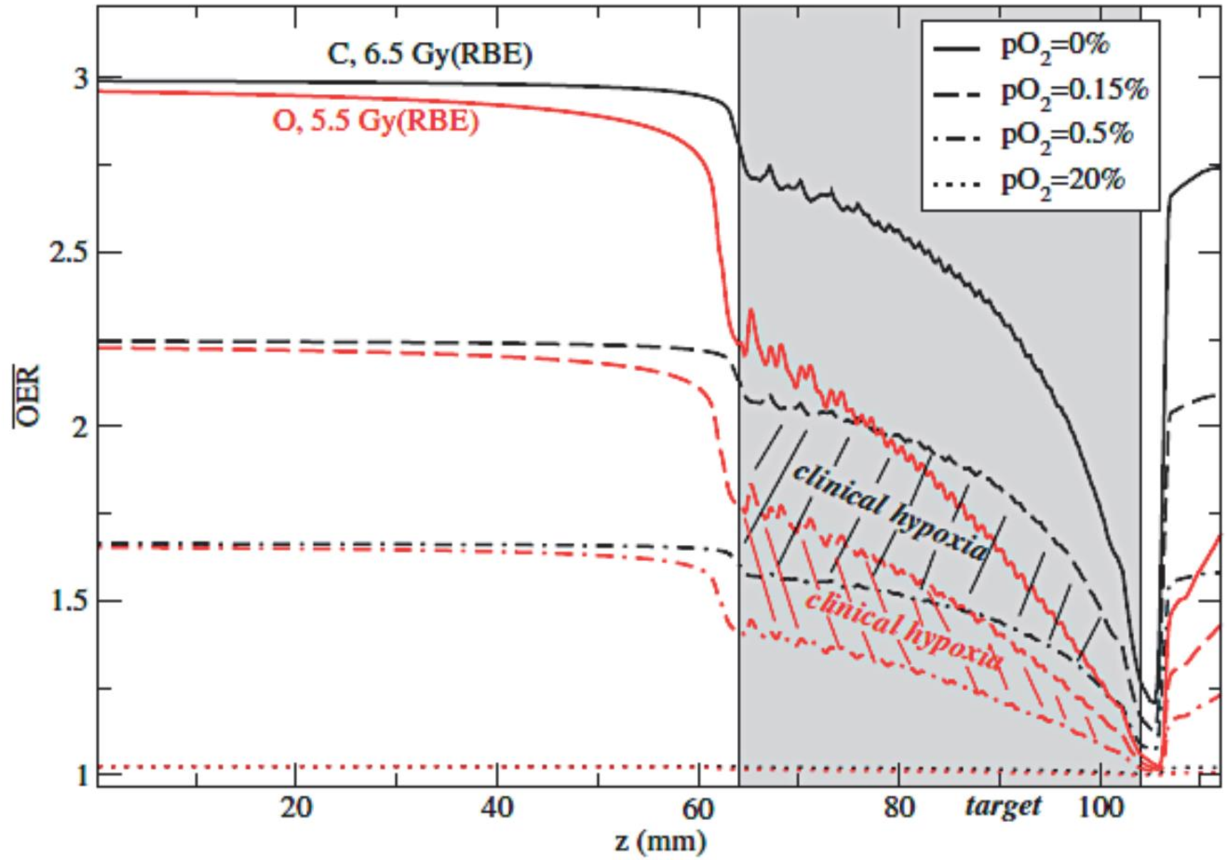
Sarcomas after definitive R1 resection (+ children). Lung carcinomas of medium size unsuitable for surgery. Prostate adenocarcinomas locally aggressive. Head and Neck locally advanced squamous cell carcinoma. High grade gliomas (+ children). Gastro-intestinal tumours highly radioresistant or anatomically difficult (some pancreatic tumours, pelvic tumours....). Skull base meningiomas, unresectable. etc.
Total: > 500/y cases for 10 million inhabitants

Medical program

- Hypofractionation
  - ✓ To reduce the number of fractions and to increase the dose per fraction
  - ✓ Stereotactic Body Radiation Therapy (SBRT) (1-3 fractions – 25-30 Gy)
  - ✓ Damage of vascular endothelial cells
  - ✓ Charged particles ideal for this type of therapy
  - ✓ Very promising data with protons and ions

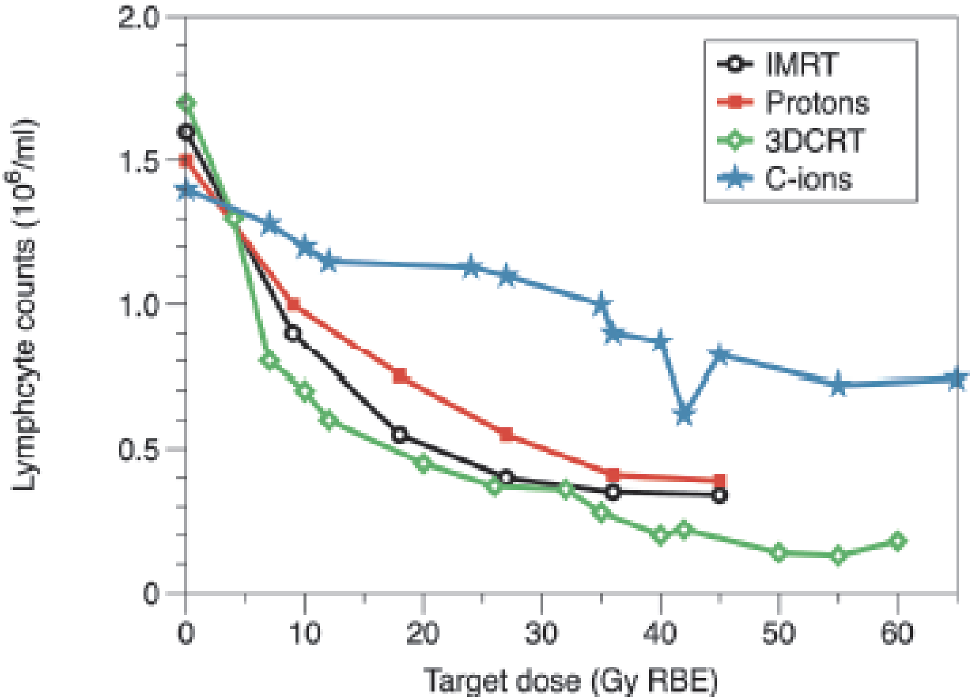
Medical program

- Hypoxia
  - ✓ To reduce the Oxygen Enhancement ratio (OER)



➢ Combined treatments

- ✓ Control of metastasis – combined radio therapy + chemotherapy
- ✓ Investigation of synergistic interaction of the drugs and ion irradiations
- ✓ Combination of particle therapy with immunotherapy
- ✓ Lymphopenia
- ✓ The imunne system suppression is reduced in the case of Protons and C-ions

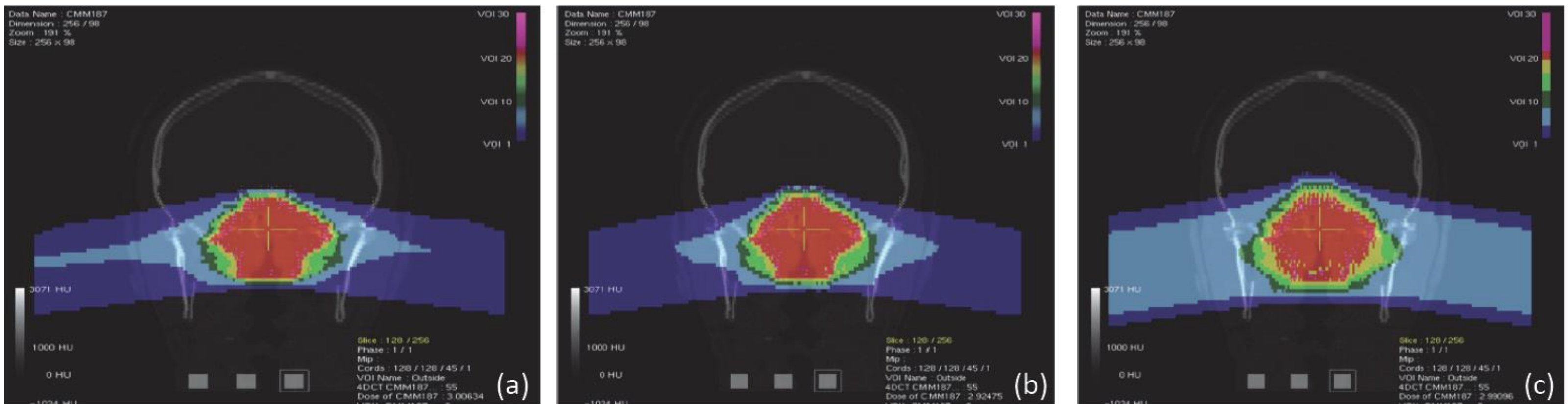


Medical program

- Radiogenomics – personalized precise medicine
  - The goal is to develop genetic risk profile - individualization of radiation dose prescriptions
    - Genetic profile determines the radiosensetivity
    - Genetic mutations of DNA repair genes induce extreme radiosensetivity
    - An example – mutations in ATM protein
  - Participate in the DNA repair and cell cycle control (G1/S)
  - Tumor tissues
    - Biomarker signatures
    - Response is highly variable

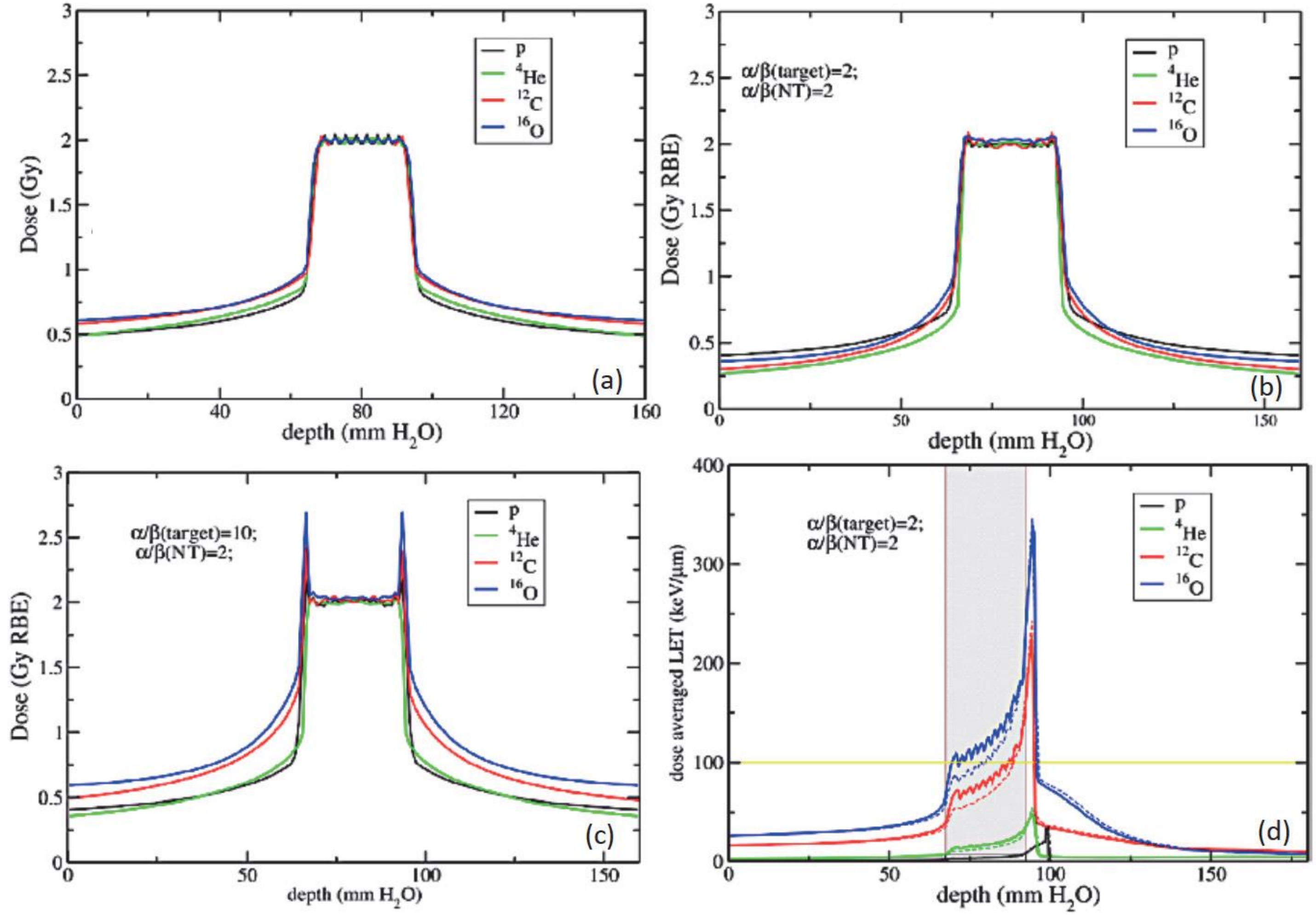
Medical program

- Therapy with other ions
  - ✓ Currently on protons and C-ions
    - He versus protons (less lateral scattering)



Medical program

- Therapy with other ions



SEE IIST
South East European International Institute for Sustainable Technologies

Treatment cost

Cancer	Fraction proton	Cost for proton	Fraction Carbon ion	Cost for carbon ion	Cost for proton + carbon ion
Breast	18,18	25.754	9,44	13.376	17.090
Prostate	23,92	33.888	23,04	17.054	22.104
Lung	32,85	46.547	16,77	23.765	30.599
Head and neck	29,77	42.176	15,18	21.503	27.705
Rectum	22,01	31.178	11,10	15.731	20.365
Pancreas	28,88	40.918	14,14	20.032	26.298
Eye	4,4	6.234	2,2	3.117	4.052
Chordoma	31,8	45.060	17,6	24.939	30.975
Liver	28,14	39.878	14,25	20.188	27.523
Gyn cancer	40	56.680	20	28.340	36.842
Hodgkin lymphoma	17	24.089	9	12.753	16.153
Meningiomas	28	39.676	14	19.838	25.789
Sarcoma	29	41.093	15,14	21.450	27.343
Gliomas	28	39.676	14	19.838	25.789
Esophageal	28	39.676	14	19.838	25.789

Total cost for proton: 38.832 EUR; Total cost for carbon ion: 19.814 EUR; Total cost for carbon ion + proton: 25.519 EUR

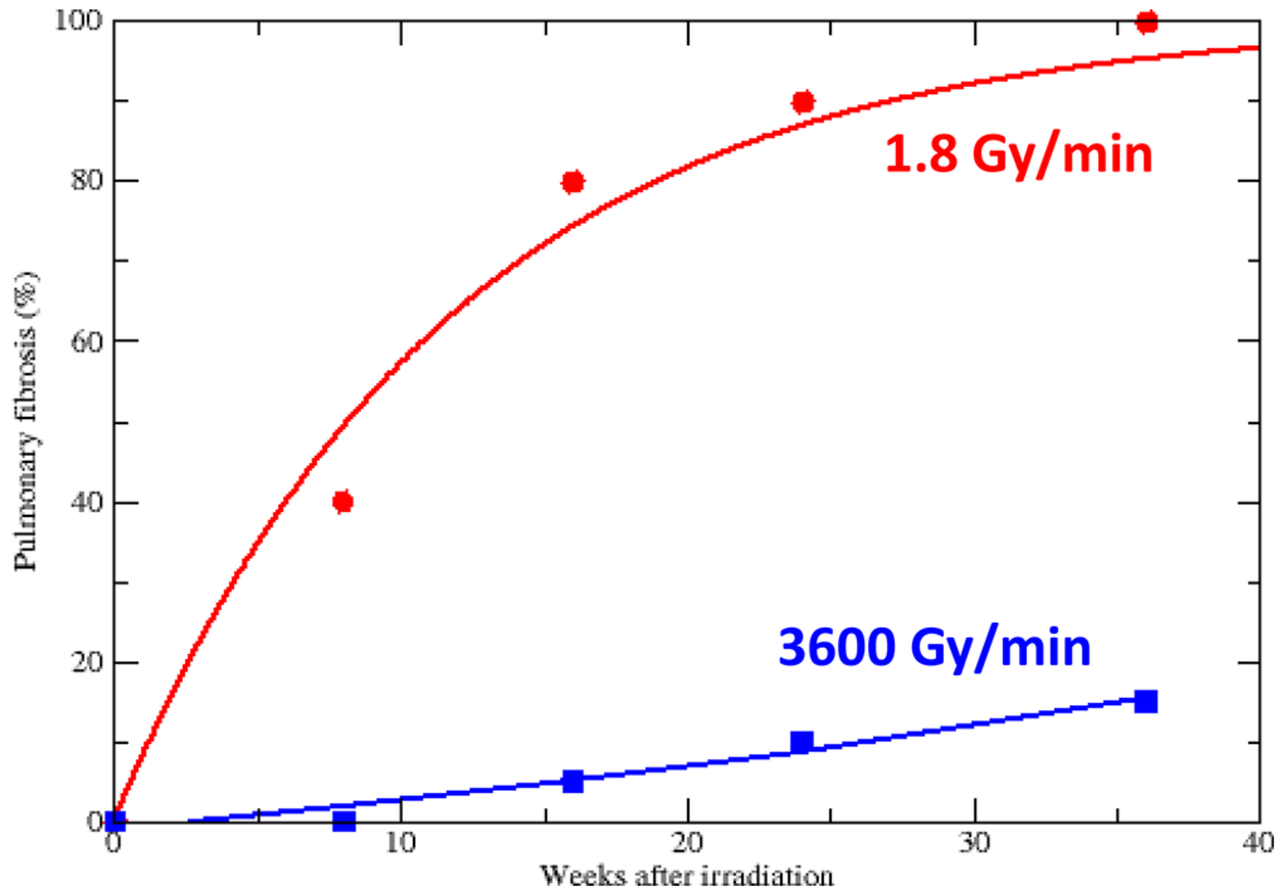
SEEIIST accelerator

Injection/Acceleration	Unit					
Particle after stripping		p	$^{4}He^{2+}$	$^{12}C^{6+}$	$^{16}O^{8+}$	$^{36}Ar^{16+}$ (*)
Energy	MeV/u	7				
Magnetic rigidity at injection	Tm	0.38	0.76	0.76	0.76	0.86
Extraction energy range (**)	MeV/u	60 – 250 (1000)	60 – 250 (430)	100 - 430	100 - 430	200 – 350
Slow extraction spill duration with multi-energy operation	s	0.1 – 60				
Fast extraction	s	$< 0.3\ 10^{-6}$				

- Warm magnets with improved design
- Fast and slow beam extraction
- Possibility for Flash therapy
- First ion accelerator in the world for FT

Towards flash therapy

- What is flash therapy
- Ultra short irradiation time (< 500 ms)
- Very high dose intensity 20 – 2000 Gy/s
- The healthy tissue is less affected



Pulmonary fibrosis in mice

Towards flash therapy

- First patient treatment
- 5.6 MeV linac electrons
- 15 Gy
- 10 fractions
- Pulses in 90 ms
- Multiresistant tumor


Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment of a first patient with FLASH-radiotherapy

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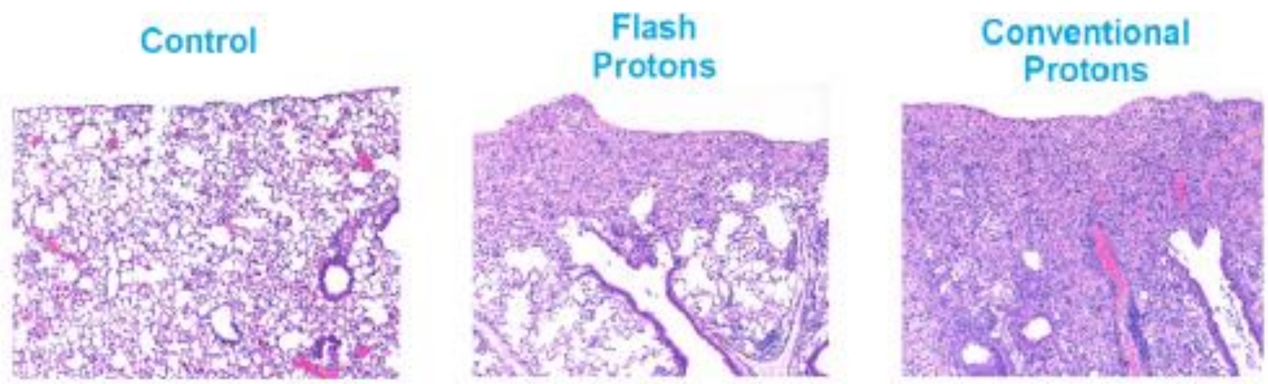
1a : Day 0

1b : 3 weeks

1c : 5 months

Towards flash therapy - protons

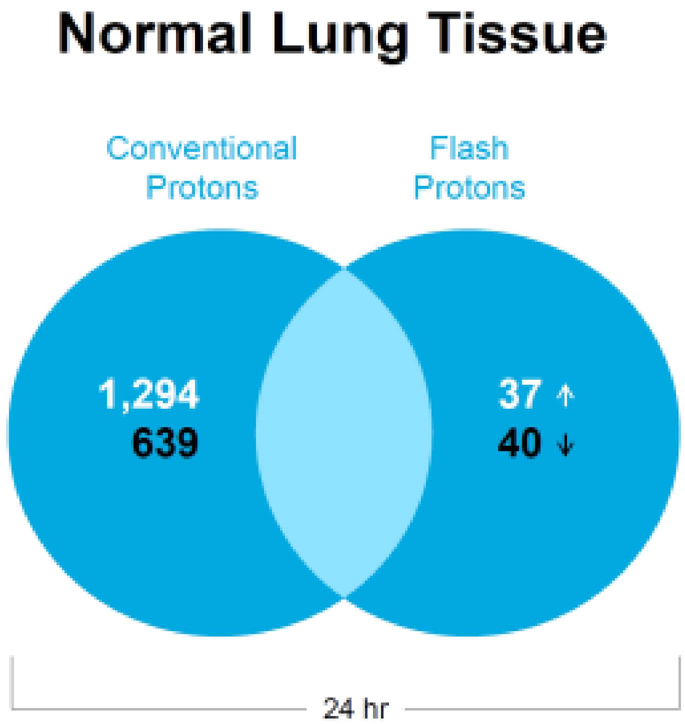
- Varian FlashForward Consortium
- 17.5 Gy in flash mode
- 25% reduction in fibrosis versus conventional
- 35% reduction in dermatitis



Lung fibrosis

Towards flash therapy - protons

- Varian FlashForward Consortium
- Flash reduces differential gene expression
- Flash protons – gene expression close to the non irradiated sample



Lung fibrosis

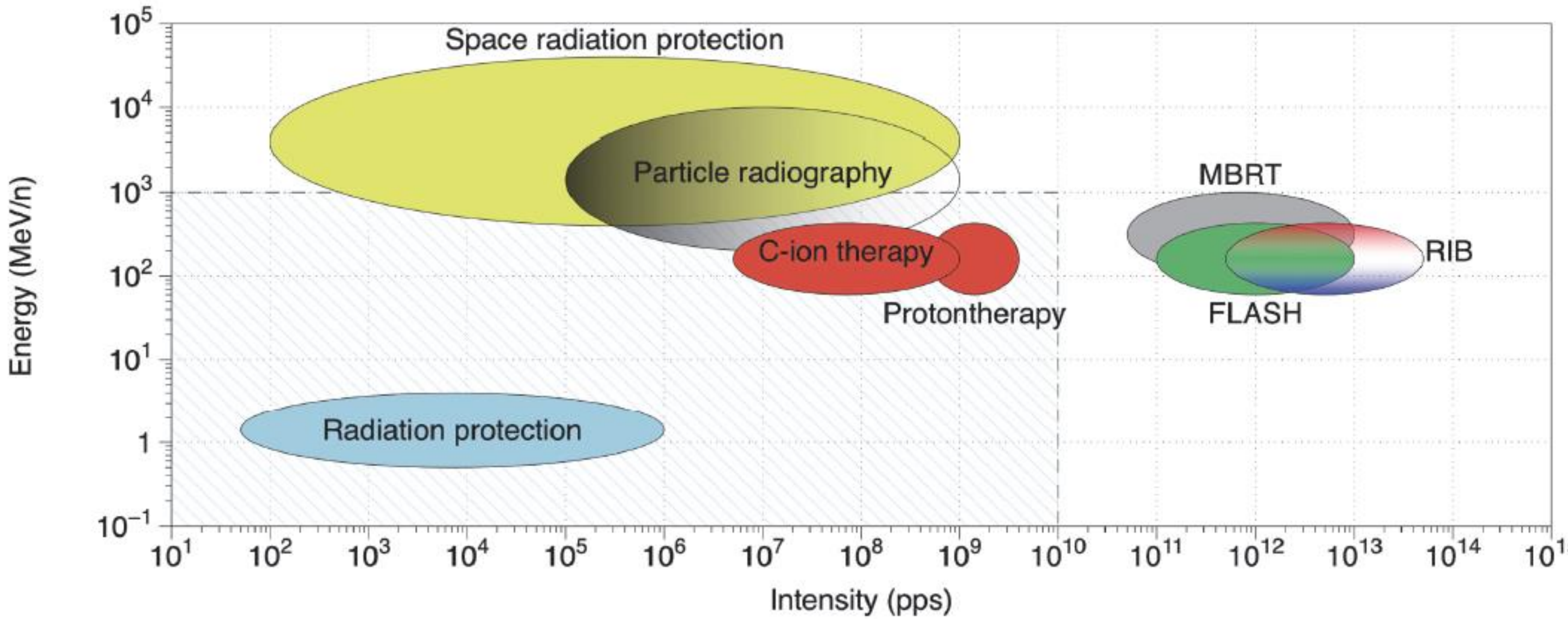
Radiobiological program

- In vitro and in vivo radiobiology
  - ✓ Increased proton RBE at the end of the range –should it be considered in the treatment planning?
  - ✓ Interplay between partial volume and RBE effects – requires in vivo investigation
  - ✓ Systematical study of combination with stimulation of the immune system
  - ✓ Stem cells radiosensetivity
  - ✓ Drugs, nanoparticles and other agents modify the radiation response.
  - ✓ Influence of the radiation on cells migration
  - ✓ Experimental data for biophysical models used for therapy planning
  - ✓ Investigation of the probability for secondary cancer induction
  - ✓ FLASH therapy mechanism

Radiobiological program

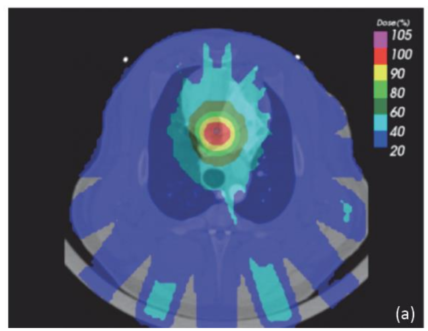
✓ Radioactive ion beams (beam visualization)

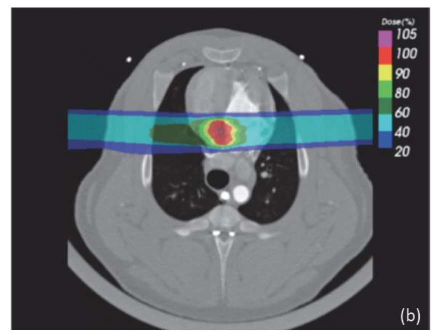
Target	Nuclear reaction channels	β^+ isotopes	Half-life
C	$^{12}C(p,pn)^{11}C$, $^{12}C(p,p2n)^{10}C$	^{10}C, ^{11}C	19.29 s, 20.33 m
N	$^{14}N(p,2p2n)^{11}C$, $^{14}N(p,pn)^{13}N$, $^{14}N(p,n)^{14}O$,	^{13}N	9.96 m
O	$^{16}O(p,pn)^{15}O$, $^{16}O(p,3p3n)^{11}C$, $^{16}O(p,2p2n)^{13}N$, $^{16}O(p,p2n)^{14}O$, $^{16}O(p,3p4n)^{10}C$	^{14}O, ^{15}O	70.61 s, 122.24 s
P	$^{31}P(p,pn)^{30}P$	^{30}P	2.50 m
Ca	$^{40}Ca(p,2pn)^{38}K$	^{38}K	7.64 m



Animal program

- Animal facility
- Small animals
  - xenografts models of tumors – small animals (rodens)
  - Suppressed immune reaction
  - Establish in- house small animal facility
  - Accept a small animals from outside
  - Investigate different protocols and trace short and long term effects
  - Animal facility close to the experimental area
- Big animals
  - External veterinary
  - Dogs and cats with tumors





  - Swine – treatment of cardiac arrhythmias

Research Program

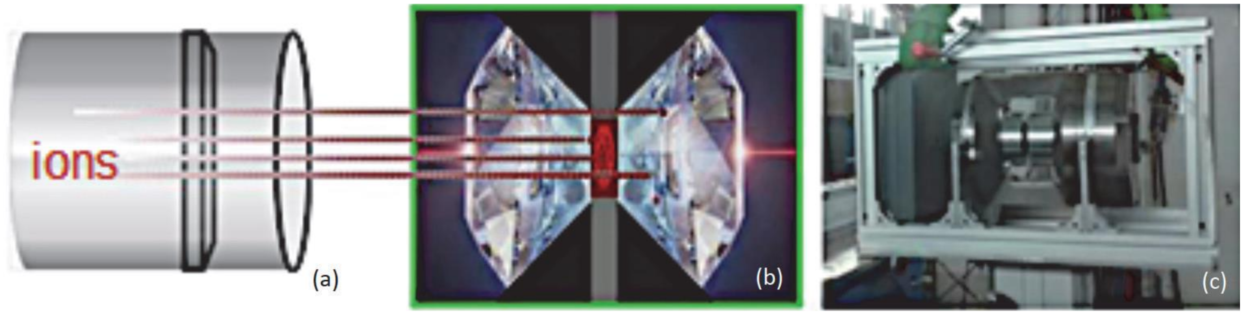
- Medical Physics
  - ✓ Flash therapy of moving organs
  - ✓ Tomography with helium ions
  - ✓ Ion acoustic imaging
  - ✓ In beam MRI – real-time information
- Material science
  - ➢ Test of radiation hardness of shielding materials
  - ➢ Space microelectronics
  - ➢ Production of nanotubes

Medical physics program

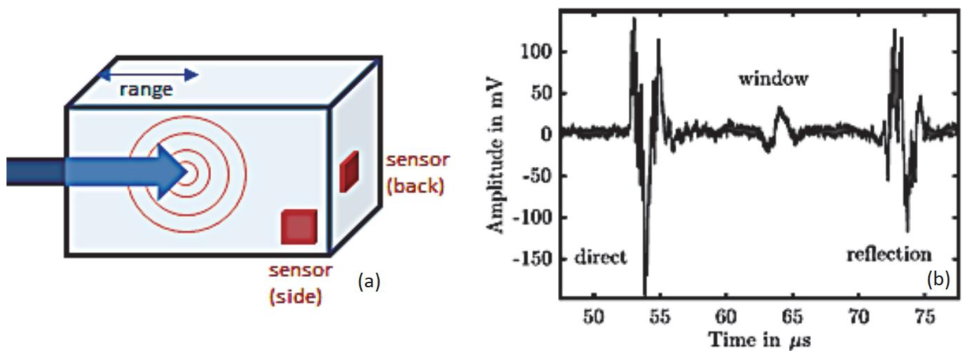
- ➢ Imaging Modalities, Motion Management and Quality Assurance
  - ✓ Measurement of leaving tissue stopping power
    - ✓ Proton or Helium tomography
  - ✓ Accuracy of dose deposition
    - ✓ Gamma cameras, PET
  - ✓ Tracking of moving organs
    - ✓ MRI, ultrasound scanners
- ➢ Biophysical modeling
  - ✓ At macroscopic and microscopic scale simulation
  - ✓ Development of clinical treatment planning systems
  - ✓ Big data analysis and development of new treatment protocols
  - ✓ Parallel processing and HPC, use of AI

Material science program

- ➢ Irradiation of materials under high pressure
  - ✓ May cause drastic changes in the properties

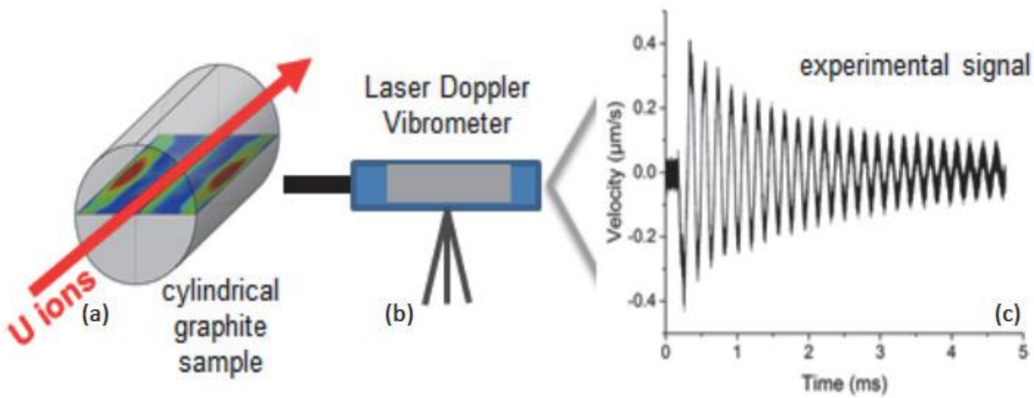


- ➢ Ionoacustic phenomena
  - ✓ Energy deposed by the ion beam (at Bragg Peak) creates ultrasound waves
  - ✓ Obtain information on internal structure
  - ✓ Ion therapy – localize the Bregg peak



Material science program

- Radiation hardness
  - ✓ Shielding, beam dumps etc at new accelerators like FAIR, European Spallation Source (ESS), HL-LHC and FCC at CERN, fusion and fission reactors
  - ✓ Beam intercepting devices – collimators, beam dumps, production targets etc.
  - ✓ New materials – at extreme doses



  - ✓ Thermal stress waves measurement

Research Program

- Radiobiology
  - New therapy solutions
    - ✓ Radio therapy with immunotherapy
    - ✓ Radio-genomics for personalized medicine
    - ✓ Ultra-high dose rate (FLASH therapy)
    - ✓ Mini-beam radiotherapy (MBRT)
    - ✓ Basic radiobiology
- Animal studies
  - Animal models for the radiobiology studies - rodents
  - Treatment of large sick animals
  - Comparative trials in pets

Medical physics program

- ➢ Beam characterization
  - ✓ Stopping power and range measurement
  - ✓ Fragments cross sections measurement (ToF , Medipix)
  - ✓ Evolution of the beam spot size along the trajectory
- ✓ Dose delivery
  - ✓ Scanning pencil beams require precise control
  - ✓ Moving organs
  - ✓ Flash therapy
  - ✓ Scanning micro beam