CERN Baltic Group

Draft concept-paper

Advanced Particle Therapy Center for the Baltic States

Background

This concept-paper is prepared following the collegial decision of the CERN Baltic Group (CBG) General meeting of 23 August 2021 "To develop a concept-paper on **Advanced Particle (Cancer) Therapy Center** in the Baltic States, in close cooperation with CERN and relevant stakeholders".

During the 23 August general meeting, based on the previous discussions, the CBG has reiterated a clear need for one **strategic regional research project** related to the (so far *de facto* non-existent) major Research Infrastructure undertaking in the Baltic States. General meeting unanimously agreed that a very good candidate for this is the Advanced Particle Therapy Center in the Baltic States. It has been agreed to elaborate in this direction and to initiate an open discussion between CBG and CERN, also engaging stakeholders from Baltic medical physics, radiotherapy, and oncology communities[1].

Such meeting "Advanced particle therapy options for Baltics" was organised in liaison with CERN on 8 October 2021[2]. Meeting agreed that the best possible option for the Baltic States would be development of the "**The Helium synchrotron**" technology in collaboration with CERN.

During the subsequent CBG General meeting on 22 November 2021 "a **need for the joint CBG flagship project** and joint coordinated actions was emphasised. CBG shall build on its success and use the momentum of Estonia and Latvia joining CERN". Meeting agreed "to persuade the idea of the potential Flagship project - **Advanced Particle (Cancer) Therapy Center in the Baltic States**, in close cooperation with CERN and relevant stakeholders".

This concept has been also presented to the Baltic Assembly[3] at CERN on 8 Oct 2022. Idea was presented to LIAA and EM in Brussels – full support received. Idea was presented to the ministry of education and science of Latvia – summer 2021

Chairman of the CERN Baltic Group
Prof. **Toms Torims**

[1] https://indico.cern.ch/event/1067091/attachments/2294085/3958931/CBGSummary7th_meeting_.pdf
[2] https://indico.cern.ch/event/1071872/
[3] https://indico.cern.ch/event/1117311/

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Current status

Current iteration of this concept paper should be taken as a draft, with the scope mainly addressing key technological concepts, physical and medical rationales for the purpose of the facility and proposed innovation and research pathways. The technological aspects within the scope of this draft concept paper are closely related and mainly drawn from the work within CERN based collaboration – **NIMMS (Next Ion Medical Machine Study)**. Within the NIMMS collaboration a dedicated **Helium synchrotron design** working group has been developed with collaborations and inputs from Baltic States scientists. The first results of the proposed helium synchrotron design are to be presented at IPAC22[4] (13th International Particle Accelerator conference), with key technological concepts of the work mentioned within the scope of this concept paper. Both the next iterations of this concept paper, moving to technical design, and technical design of Helium synchrotron are to be done with collaborations from Baltic States scientific community.

Current iteration of this concept paper has been presented:

- 21st meeting of the TIARA Collaboration Council (March 29th , 2022)[5]
- 9th CERN Baltic Group General Meeting (April 12th, 2022)[6] with **draft concept paper being approved by CERN Baltic Group**
- Among NIMMS Helium synchrotron design working group, **receiving approval of draft concept paper on behalf of NIMMS collaboration leader Dr. Maurizio Vretenar**

[4] Paper in preparation for IPAC22: **M. Vretenar**, E. Benedetto, M. Sapinski, M. E. Angoletta, G. Bisoffi, J. Borburgh, L. Bottura, K. Paļskis, R. Taylor, G. Tranquille: *A Compact Synchrotron for Advanced Cancer Therapy with Helium and Proton Beams*

[5] https://indico.cern.ch/event/1137672/ [*protected*]

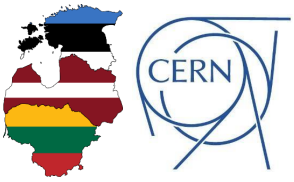
[6] https://indico.cern.ch/event/1138329/

CERN Baltic Group

Draft concept paper

Advanced Particle Therapy Center for the Baltic States

Technical concept: Short overview and introduction



Proposal of the conceptual design

The overall conceptual idea of Advanced Particle Therapy Center in Baltic States stands not just as a clinical cancer treatment center, but as a strong research institution providing rich infrastructure for new scientific research fields and possibilities. The main idea of Advanced Particle Therapy Center in Baltic States is a unification of three main functions that are closely interdependent:

- a cancer treatment clinic providing completely novel advanced particle therapy solution – helium ion therapy, which is a complete clinical novelty currently undergoing clinical trials, with highly promising results, only at one of Europe's largest particle therapy centers – Heidelberg Ion-Beam Therapy Center (HIT). Along with radiotherapy possibilities within the nuclear medicine field can be accomplished – targeted radionuclide therapy, theranostic approaches and advanced cancer diagnostics and treatment response estimation capabilities;
- a multi-disciplinary research institution, covering not only the clinical and pre-clinical research needs for radiation oncology and nuclear medicine, but also opening possibilities for research in the fields of medical physics, accelerator physics, accelerator technologies, material sciences, radiochemistry and others;
- a facility within the Baltic States providing the necessary infrastructure for fostering of novel particle accelerator technology innovation and development with the involvement and close collaborations with the local industry sectors.

The proposal further provides main rationales behind the proposed functions, while also providing detailed descriptions of various aspects in annexes.

The scope of the proposed Advanced Particle Therapy center can be successfully accomplished only through a close collaboration of scientific, industrial and medical sectors within the Baltic States, therefore the project proposal and full support comes from **CERN Baltic Group**. CERN Baltic Group unifies the main stakeholders in the respectively aforementioned sectors within the Baltic States region, which therefore provides the necessary expertise and support in carrying out a project of such a scope.

Physical rationale of particle therapy

Radiation therapy is the use of ionizing radiation to target DNA of cancerous cell in order to induce cellular death or limit further multiplication of cancerous cells, effectively limiting further spread of the tumor. The most prevalent radiation therapy method in clinical use is the usage of linear electron accelerators in order to produce high energy photon therapeutic beams. Due to physical interaction mechanisms with matter, high energy photon beams in general do not provide favourable energy deposition as the maximum energy is deposited at shallow depths near the surface, thus requiring multiple beams and exposing larger volume of healthy tissue to ionizing radiation.

Since 2000's a lot of clinical focus has been gained by charged particle or so-called 'hadron' therapy – use of proton or heavier ion beams for cancer treatment. Because of their electric charge, particles as protons interact with matter very differently from high energy photon beams, providing the main physical advantage in the form of so-called 'Bragg peak' – maximum dose is deposited at a certain, energy dependent depth, while dose deposited proximal and distal to this peak is minimal. Moreover, as 'charged particles' ionize the matter more densely than high energy photons, protons also possess a relatively increased biological effect compared to conventional therapy.

Use of 'heavier hadrons' such as carbon ions comes with even more localized dose deposition and increased biological effect, overcoming cellular oxygen dependency in hypoxic tumors. Though, as carbon ion treatment requires more expensive particle accelerator systems, a lot of clinical interest has been lately focused on helium ions, that could provide the 'golden optimum' between protons and carbon ion characteristics. With these optimal physical characteristics, at present helium ions are undergoing clinical research for full integration as a cancer treatment modality.

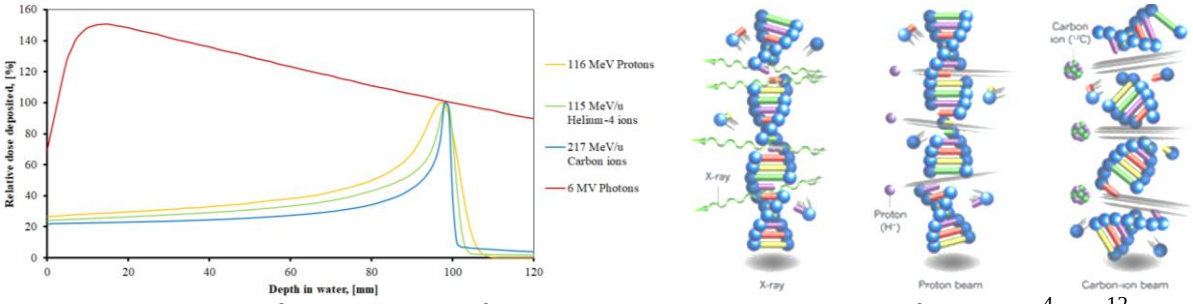


Figure 1. *on the left* Comparison of dose deposition characteristics of protons, ^{4}He, ^{12}C and high energy photons
on the right Schematic representation of different particle capabilities of damaging DNA

Novel paths of nuclear medicine

Nuclear medicine uses radioactive isotopes for diagnostic or therapeutic purposes or in the novel combined approach – theranostics. Large part of radioisotopes for nuclear medicine are generally produced by particle accelerators – cyclotrons, but within the scope of this proposed facility a linear accelerator used for injection into therapy synchrotron will be used for radioisotope production, providing novel and more efficient production options for specific radioisotopes that require 'niche' particle beams – α particles and deuterons, as such particle beam production is highly inefficient with cyclotrons.

On one hand nuclear medicine provides unparalleled functional imaging capabilities in radiation oncology for tumor detection. On the other hand, nuclear medicine provides novel treatment options for oncological malignancies, with an important field of therapeutic nuclear medicine being the targeted α-emitter therapy – use of α emitting radionuclides in radiopharmaceuticals for localized cancer therapy. Various preconditions regarding the properties of decay must be fulfilled, in order to consider an isotope effective for targeted α-emitter therapy and one such isotope is astatine-211 (^{211}At). Astatine-211 can be produced by 'bombardment' of bismuth targets with α particle beams, that can be done more efficiently with the proposed linear particle accelerator design for this facility, compared to cyclotrons because of the associated α-beam extraction losses.

Novel field in nuclear medicine is the so-called 'treat what you see' approach – theranostics. For theranostic approach either the same chemical element isotope pairs with both diagnostic and therapeutic decay properties are used or isotopes that can undergo both decay types. For the facility's proposed radioisotope production with a linear accelerator, possibilities of theranostic nuclear medicine can be realized by production of copper-64 and copper-67, tin-117m, samarium-153 and rhenium-186.

Clinical gains and possibilities of particle therapy and nuclear medicine

Based on the outlined physical characteristics of proton and helium ion beams, the most important clinical applications are in the field of paediatric oncology – as the modern technological advancements of radiation therapy increase the overall survival of paediatric

patients, it becomes of uttermost importance to limit exposure of the healthy, developing tissue to ionizing radiation in order to decrease late side effects and tissue growth defects, which can be done more effectively with proton and helium beams.

Owing to the more localized dose deposition, proton and helium beams provide more efficient treatment option than conventional high energy photon therapy in cases, where tumor is close to critical organs – brain tumors and head and neck region. Proton and helium therapy is also an efficient radiation therapy treatment for oncological malignancies of central nervous system, eyes, liver, lung, prostate, gynaecological and gastrointestinal localizations.

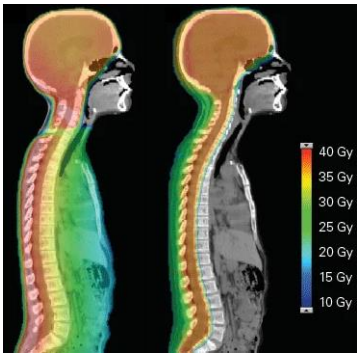
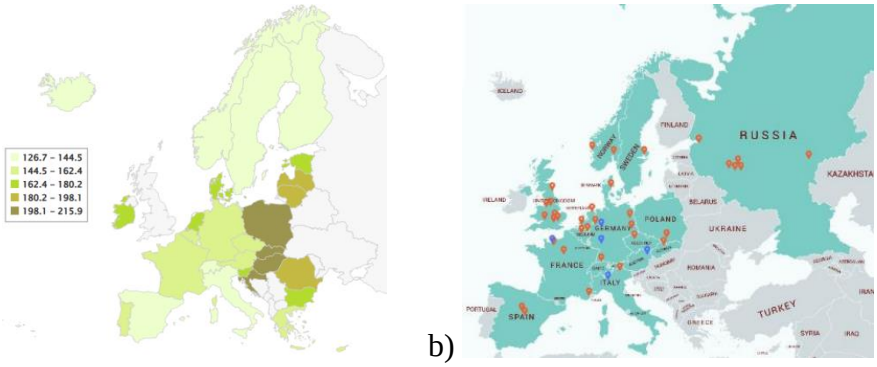


Figure 2. Comparison of dose distributions for medulloblastoma treatment for a paediatric patient
(*left* – treatment with high energy photons, *right* – treatment with charged particles)

On the other hand, nuclear medicine provides diagnostic capabilities for detection of cancerous cells, providing functional information useful for cancer treatment planning and allowing tumor response assessment during or after treatment. Diagnostic capabilities of radioisotopes are also being used in functional imaging for cardiology.

It must be noted, that in one out of for cases, the patient is unable to receive the necessary radiation therapy cancer treatment, with one of the main reasons being the limited availability of the necessary technologies. From statistics of cancer cases and mortality, it is evident that one of the highest cancer mortality rates in Europe are in Baltic States and Balkan states, that are also the regions in Europe that do not have cancer treatment centers, utilizing particle therapy.



a) b)

Figure 3. a) Cancer mortality rate in Europe per 100 000 inhabitants (data of 2020)
b) Map of particle therapy centers in Europe

Proposed technical design concept and industry involvement

Central part of the proposed Advanced Particle Therapy center is the **helium synchrotron** – a completely novel particle accelerator technology proposed by scientists at

CERN working within NIMMS (Next Ion Medical Machine Study) collaboration project. Helium synchrotron would be a completely novel particle therapy system – „first of the kind" – expanding the clinical possibilities compared to protons, while reducing the dimensions and technological complexity that is necessary for a carbon ion therapy facility. Helium synchrotron conceptual design is currently in an active development stage with the concept design ready in summer of 2022, that would be followed by a technical design development in 2022 and 2023, that would be done with contributions from CERN Baltic Group scientific institutions.

As already stressed, helium synchrotron is a design developed by CERN, therefore CERN is one of the most crucial partners in delivering the proposed Advanced Particle Therapy center of Baltic States. CERN already has an extensive experience in developing the design of particle therapy treatment center designs, as before the NIMMS collaboration, the CERN based collaboration project PIMMS (Proton-Ion Medical Machine Study) developed the necessary technologies of particle therapy machines that were adopted in design and construction of two particle therapy centers in Europe: MedAustron (Austria) and CNAO (Italy).

The main idea of NIMMS collaboration is the design and development of novel particle therapy machinery solutions, such as helium synchrotron, while leaving it open for project partners and collaborators to use these technologies for assembly of an individualized facility. CERN Baltic Group can fully embrace the close collaboration in this field as the scientific personnel of CERN Baltic Group is already involved and delivering contributions to NIMMS project.

The main parts of the proposed Advanced Particle Therapy center in Baltic States infrastructure are:

- linear accelerator for particle injection into synchrotron, providing parallel production of radioisotopes;
- ion source for helium ions and protons;
- synchrotron designed for helium ions;
- two beamlines for patient treatment – one fixed horizontal beam line and one with a rotating gantry based delivery system;
- one research beamline.

The proposed facility would be the first in Baltic States, having an extensive particle accelerator system, that could foster innovations in particle accelerator technologies and provide pathways for industrial involvement from Baltic States in production of particle accelerator components and support systems. Moreover, based on the novelty of the helium synchrotron technology – Advanced Particle Therapy center of Baltic States would be the first of the kind.

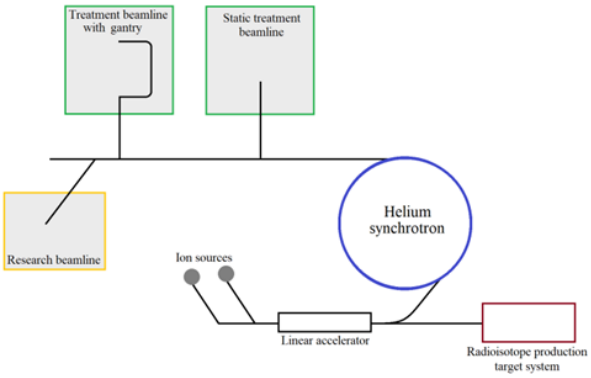


Figure 4. Schematic overview of the proposed facility's design

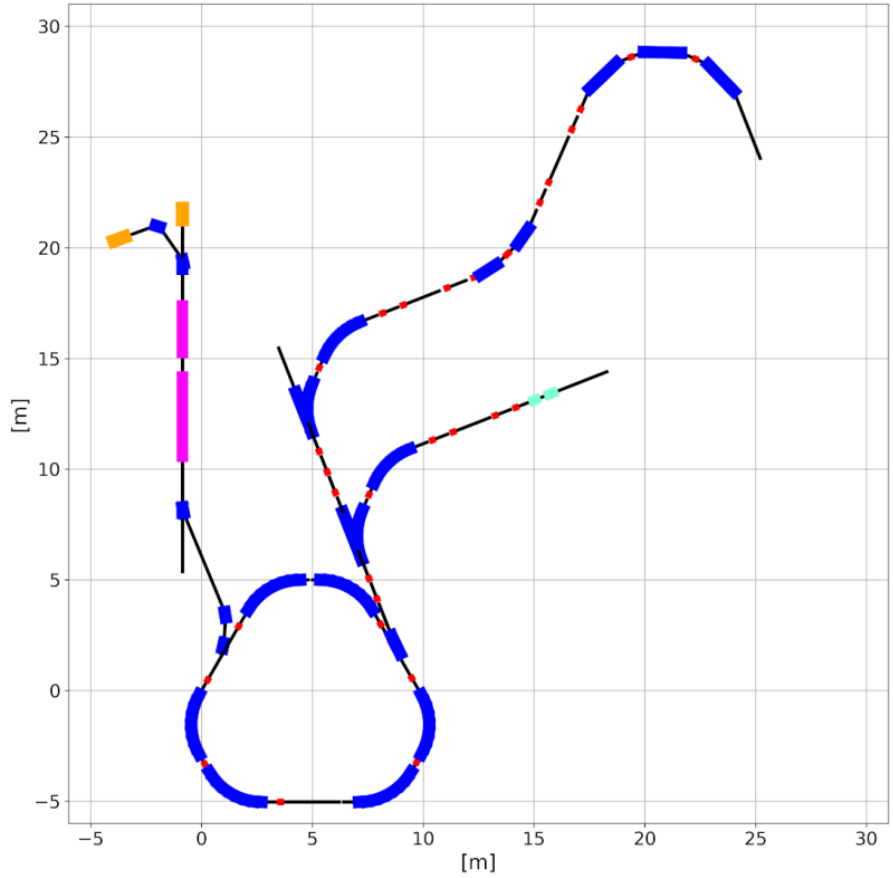


Figure 5. Scaled layout of the proposed accelerator complex lattice design[7]

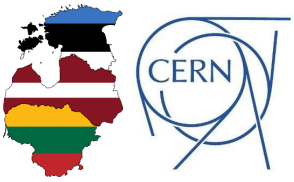
Concerning the proposed operation of the proposed facility, it would be divided in two phases: **initial phase** and **clinical use phase.** In the initial phase of the facility 50% of the beam time would be dedicated to patient treatment with clinically approved protons, while 50% would be dedicated to research with helium ions. The clinical use phase would commence, when helium ion treatment is clinically approved, and then 25% of the beam time could be dedicated to patient treatment with protons, 50% - patient treatment with helium ions and the remaining 25% of the beam time would be dedicated to research with helium ions.

Novel scientific research directions

The novelty of helium synchrotron design provides not only completely new clinical pathways and industry involvement in technological development and delivery, but also a plethora of new research directions that are completely novel in Baltic States. Even more importantly, considering the uniqueness and novelty of helium ion therapy, Advanced Particle Therapy center in Baltic States would provide a world level clinical research infrastructure for a completely novel treatment modality.

With the proposed infrastructure of the facility the main research areas would be in the fields of accelerator physics, accelerator technology, medical and biophysics, radiation oncology pre-clinical research and clinical trials, nuclear medicine, material sciences and others. As a scientific research institution Advanced Particle Therapy center in Baltic States

[7] Design created by **Mariusz Sapinski (GSI/SEEIIST)** with Maurizio Vretenar (CERN) and Elena Benedetto (SEEIIST/CERN)



would provide collaborations with universities of Baltic States and other international partners allowing 'beam time' on the dedicated research beamline for specific research projects.

Scientific research activities of the center would also be closely linked to the clinical functions of the facility as many of the proposed fields of study could provide results for more effective and novel radiation therapy treatment options, mainly concerning the necessary clinical research for full scale helium ion treatment regime, very high dose rate treatment or so-called *FLASH* and medical physics related studies with the overall goal to increase cancer treatment planning precision. Importantly, *FLASH* therapy with helium ions also stands as complete novelty.

For scientific research purposes, helium synchrotron design can also provide a carbon ion beam that could be used pre-clinical research, studies of *FLASH* therapy with carbon ion beams and of carbon ion fragmentation for improved treatment planning precision.

All of the proposed research directions closely correspond to identified necessities and current pitfalls in a recent study[8] within particle therapy community regarding helium ion therapeutical usage possibilities. Thus, providing a framework and research facility as proposed, international scientific collaborations could be developed and results of worldwide interest could be achieved for this novel and emerging cancer treatment modality.

[8] Mairani A, Mein S, Blakely EA, Debus J, Durante M, Ferrari A, Fuchs H, Georg D, Grosshans DR, Guan F, Haberer T, Harrabi SB, Horst F, Inaniwa T, Karger CP, Mohan R, Paganetti H, Parodi K, Sala PR, Schuy C, Tessonnier T, Titt U, Weber U. "**Roadmap: helium ion therapy**", *Phys Med Biol*., 8. Apr 2022, doi: 10.1088/1361-6560/ac65d3

CERN Baltic Group

Draft concept-paper

Advanced Particle Therapy Center for the Baltic States

Technical concept: Detailed rationales and aspects

Physical aspects of charged particle therapy

As a cancer treatment modality radiation therapy is essentially the use of ionizing radiation for targeting the DNA of tumor cells in order to induce cellular death (apoptosis) or limit further cellular multiplication and spread. The main clinical rationale of radiation therapy is delivering high dose level to cancerous cells in order to increase tumor control probability (TCP), while keeping normal tissue exposure to radiation as low as possible – decreasing normal tissue complication probability (NTCP). Considering the interplay between TCP and NTCP curves the, so-called, „complication free" region.

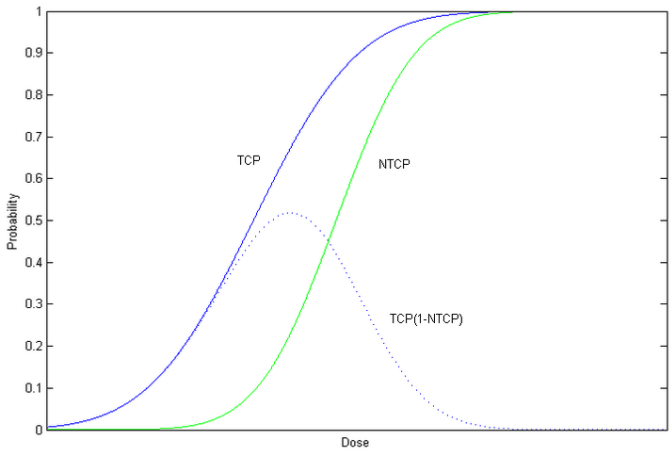
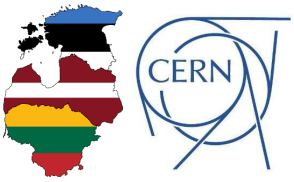


Figure 1. Example of TCP and NTCP curves with a representation of „complication free region" (*dashed line*)

Most common clinical method of radiation therapy is the use of external beams of high energy photons, with the energies being around few megaelectronvolts (MeV). Such high energy photon beams are produced by linear electron accelerators, where a beam of electrons is accelerated to energies between 6 to 10 MeV and then strikes a target made of a material with high atomic number, typically tungsten, producing the photon beams. Photon beam is further shaped either by blocks or multi-leaf collimators, in order to match the radiation field for the specific tumor.

When interacting with tissue, high energy photons do not ionize the matter directly - through the main physical interaction mechanism of Compton scattering, secondary electrons are produced that ionize the matter. At higher photon energies, pair-production mechanism is also possible, that also produces ionizing secondary electrons. Because of these interaction mechanisms, high energy photons deposit most of their energy close to surface and traverse further, depositing energy through secondary electrons 'along the way'. Thus to achieve optimal and acceptable dose distribution – energy deposition maximized within the tumor and minimized for healthy tissue - multiple radiation beams from various directions are used to concentrate the high dose region. Although various technological innovations have been made for external beam radiation therapy with high energy photons such as radiation field intensity modulation (IMRT), image guidance (IGRT), radiation delivery with continuous gantry rotation (VMAT) and stereotactic treatments (SRS and SBRT), the capabilities of high energy photons are limited by the mentioned physical aspects:



- high energy photon dose deposition characteristics are not favourable, as the largest dose deposition is at shallow depths and photons can traverse tissue matter for long paths. Thus to mitigate these characteristics, multiple beams are used, which results in a larger normal tissue volume exposed to radiation;
- on a cellular level, the spatial distance between two ionization events determines the final biological effect – as the ionization events become 'denser', the biological effectiveness of the particle increases. Secondary electrons produced by high energy photon beams ionize the matter sparsely as their ionization tracks are not concentrated in small volumes – particles with low linear energy transfer (LET), thus the produced biological effect at cellular level is low.
- going further with interactions at cellular level, high energy photons and the corresponding secondary electrons mainly interact with cellular DNA through indirect action, that is, interactions with tissue and ionization events produce highly reactive free radicals that further interact with the DNA of cancerous cells. Since free radical production is dependent on the oxygen content of the cells, high energy photon irradiation is not applicable for treatment of tumors with low cellular oxygen content (hypoxic) as such tumors are resistant to photon radiation.

In years following 2000's, more and more focus has been given to the introduction of the so called 'hadron' or 'charged particle' therapy into clinical environment. This cancer treatment modality uses beams of charged particles such as protons or heavier ions instead of high energy photons. Because of the electrical charge that such particles possess, the underlying physical mechanisms for such particle interactions with matter greatly differ from high energy photons – Coulomb interactions with atomic electrons, Coulomb interactions with the nucleus of an atom and nuclear reactions. Through this interactions, protons and heavy ions continuously lose part of their initial energy and this energy deposition reaches a maximum at a certain energy-dependent depth, creating the so-called 'Bragg peak', while dose deposition before and after 'Bragg peak' is low or even neglible. Based on these physical characteristics, charged particles create far more clinically favourable dose distributions while using lesser number of differently oriented beams, thus greatly reducing dose deposition within the healthy tissue and also effectively reducing the normal tissue volume that is exposed to ionizing radiation. These dose deposition aspects, in turn, greatly reduce normal tissue toxicities and complication probabilities, therefore increasing the overall cancer treatment effectiveness. Reduction of normal tissue toxicities, to a certain level, also allow the increase of the treatment dose for an increased local control probability of the tumor, that is highly beneficial in certain cases. Proton beams also ionize the matter more densely, having an increased LET, compared to high energy photons, therefore possessing an increased biological effectiveness and achieving greater biological end-result for the same absorbed dose level.

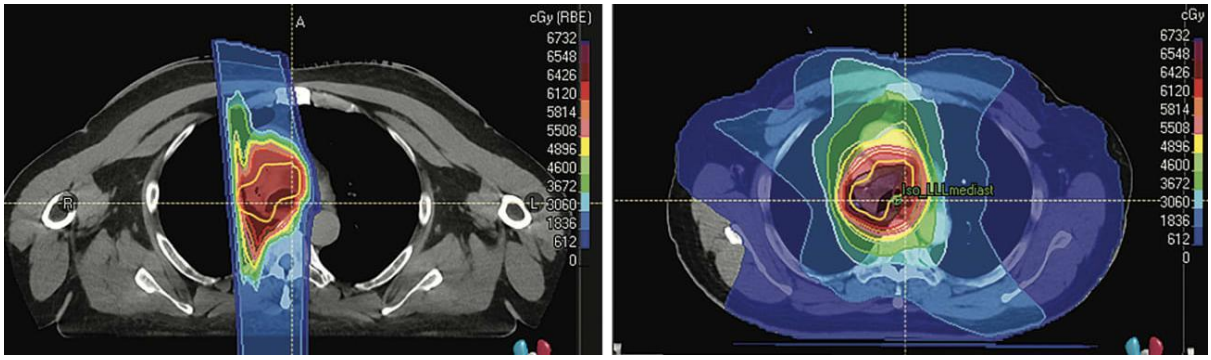


Figure 2. Comparison of dose distributions for centrally located lung cancer

left – proton treatment plan, *right* – high energy photon treatment plan

As proton therapy has already gained a place within the clinical environment by having over 120 clinics around the world, the medical community's focus is increasing towards the use of heavier particles – ions. The main advantages of heavier particle use for radiation therapy over protons again stems from the physical properties and the corresponding biological effects:

- proton beams are prone to extensive beam size broadening in lateral directions due to multiple Coulomb scattering, thus the conformality of the deposited dose to tumor volume is limited and becomes an issue for deep-seated tumors. Due to multiple Coulomb scattering, the penumbra characteristics of proton beam at large depths are even worse compared to high energy photons, thus providing gain only in low dose level reduction, while increasing normal tissue volume exposed to high dose level. Heavy ions are less prone to multiple Coulomb scattering and therefore it is possible to achieve narrower beams, thus allowing highly conformal dose deposition laterally. It should be noted, that energy and range straggling for heavier ions is also reduced compared to protons, thus achieving faster dose fall-off after Bragg peak – increased distal conformality.
- while proton beams have an increased biological effectiveness compared to high energy photon beams, this increase is still little and does not overcome the radioresistance of hypoxic tumors. On a cellular level, heavy ions are highly densely ionizing particles (with very high LET) and can directly damage DNA of cancerous cells through single or double strand breaks, thus providing greatly increased biological effectiveness and overcoming the interaction dependence on cellular oxygen content, allowing treatment of even generally radioresistant - hypoxic tumors.

Carbon (^{12}C) ions have been the main focus in heavy ion use for radiation therapy as they offer increased biological effectiveness and provide the possibility of radioresistant tumor treatment, which correspond to about 5 % of all solid tumor types. From physics perspective, a 'down-side' for carbon ion beams is the so-called 'fragmentation' – by undergoing nuclear interactions with tissue, the projectile particle 'fragments' into lower atomic number ions and these 'fragment particles' traverse beyond the 'Bragg peak' increasing the dose deposition distal to tumor – creating the so-called 'fragmentation tail'.

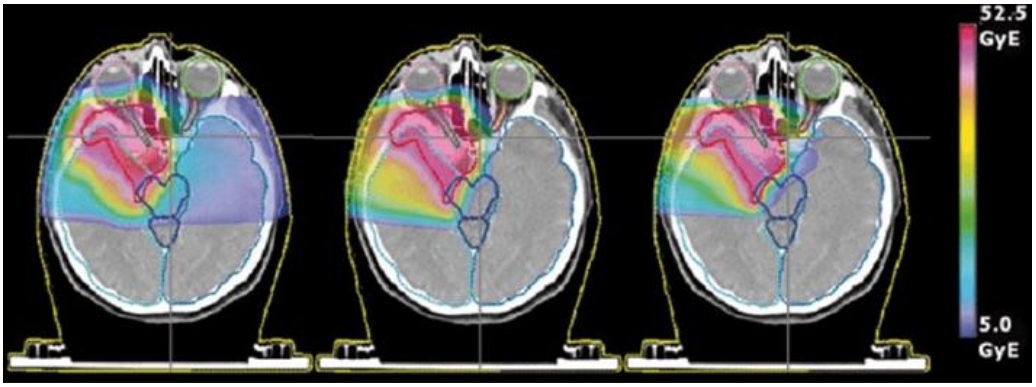


Figure 3. Comparison of dose distributions for a meningioma case

from the left – treatment plans with high energy photons, protons and carbon ions

Based on this physical aspect and greatly increased costs of particle accelerators for carbon ion compared to protons, in recent years there has been an increased interest of 'lighter ion' use for cancer treatment – helium (^{4}He) ions. Helium ions possess increased biological effectiveness and reduced lateral beam broadening compared to protons, while maintaining low level of initial particle fragmentation and the associated dose deposition distal to 'Bragg peak'. Moreover, because of generally lower linear energy transfer values of helium ions and less complex mixed beam from nuclear fragmentation reactions compared to carbon reduces the associated uncertainties of biological effect modelling that are of high importance, when considering hadron therapy treatment. Moreover, the generated neutron flux for helium ions is lower than for carbon beams, while the associated neutron biological dose could be even lower than in proton beams, therefore greatly reducing neutron radiation related risks that are of a particular importance within pediatric oncology treatments. Use of helium ions is still a clinical novelty, but has already shown clinical potential with first patients treated last year at Heidelberg Ion-Beam Therapy center (HIT), which currently remains the only ion therapy clinic in the world providing such a novel treatment. Various treatment planning studies have also shown that is possible to achieve more conformal and clinically favourable dose distributions while also reducing normal tissue toxicities with helium ion beams compared to proton beams. A particle accelerator design specifically for helium ion therapy has been proposed by the collaborators within 'Next Ion Medical Machine Study' (NIMMS) project that would allow such a novel treatment option while simultaneously allowing the clinically established proton therapy and research possibilities for carbon ion beams.

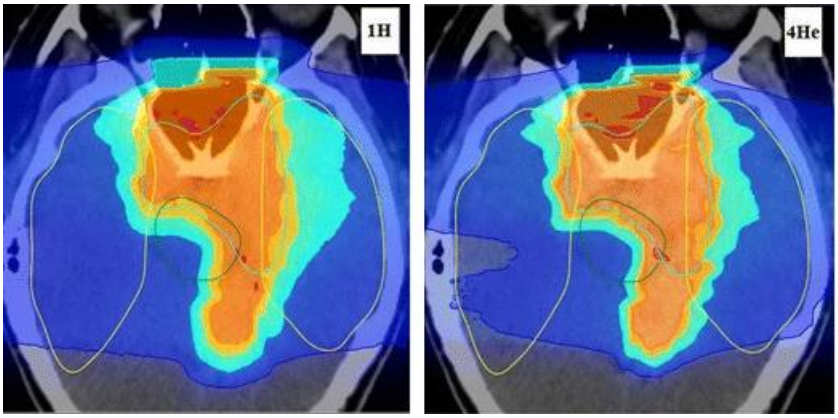


Figure 4. Comparison of dose distributions for meningioma treatment

left – proton treatment plan, *right* – helium-4 ion treatment plan with visibly reduced higher dose regions in healthy tissue

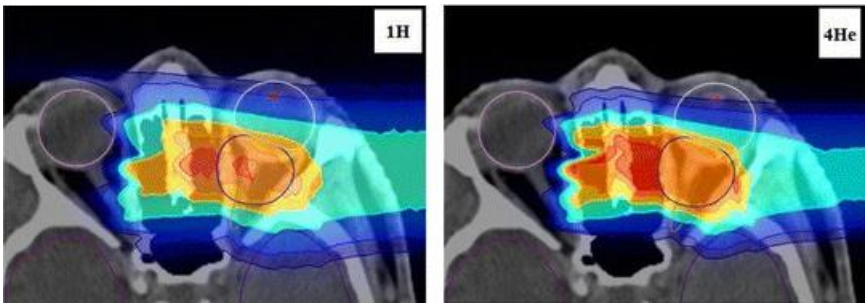


Figure 5. Comparison of dose distributions for a treatment case for a tumor near eye lens

left – proton treatment plan, *right* – helium-4 ion treatment plan with visibly reduced higher dose regions in healthy tissue

From technological point of view, proton and ion beam therapy is done in one of two ways:

- **passive beam scattering** - the initial pencil like beam is spread out laterally with use of scattering filters. Radiation field shape then is tailored to the specific tumor by use of collimators and compensators are used in order to create a composite Bragg peak with a shape that matches the distal end of the irradiated tumor volume;
- **active pencil beam scanning** – the initial pencil beam's position is actively steered with scanning magnets along the lateral extents of the treatment volume 'layer-by-layer' – by changing the initial particle energy the scanning depth is changed. This approach allows more precisely shaped dose distributions that are highly conformal to tumor volume.

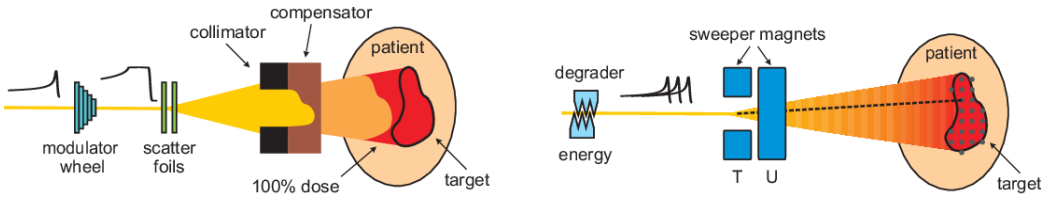


Figure 6. Schematic representation of charger particle therapy delivery techniques (*from the left* – passive beam scattering and active pencil beam scanning)

Physical and radiochemistry aspects of radioisotope production for nuclear medicine

Nuclear medicine uses radioactive isotopes for diagnostic or therapeutic applications with a even more novel approach, combining therapy and diagnostics in the so-called 'treat what you see' approach – theranostics. Radioactive isotopes for nuclear medicine are used in the form of radiopharmaceuticals, where radioactive isotopes are chemically bound with biological molecules such as antibodies or peptides. In such a way molecules of radiopharmaceuticals can target specific cell or tissue types or particular organs in order to get the diagnostic information or provide therapeutic effect at a certain location within the human body. The specifity of targeting abilities of a particular radiopharmaceutical is mainly dependent on the biological molecule used within the compound and this aspect will not be discussed in great detail for this report. Radionuclide and it's radioactive decay characteristics are the determining factors of the diagnostic capabilities or therapeutic effectiveness of a particular radiopharmaceutical:

- radionuclides, that undergo γ decay with a sufficient energy of the emitted photons or β^+ decay, can provide diagnostic capabilities with radiopharmaceutical binding at a specific functional region within the body, where it can be detected to localize this region. Radionuclides undergoing γ decay emit photons, which can be then detected to 'pinpoint' the location of emission with the technique of single photon emission computed tomography (SPECT). If a radionuclide undergoes β^+ decay, it emits a positron – an antimatter particle – which, after travelling for a short range, annihilates with a electron within the traversed matter, emitting two anti-parallel photons of the same energy of 511 kiloelectronvolts. By detecting these photons and differences in their 'arrival time' at the detector, the point of emission can be localized – technique of positron emission tomography (PET).

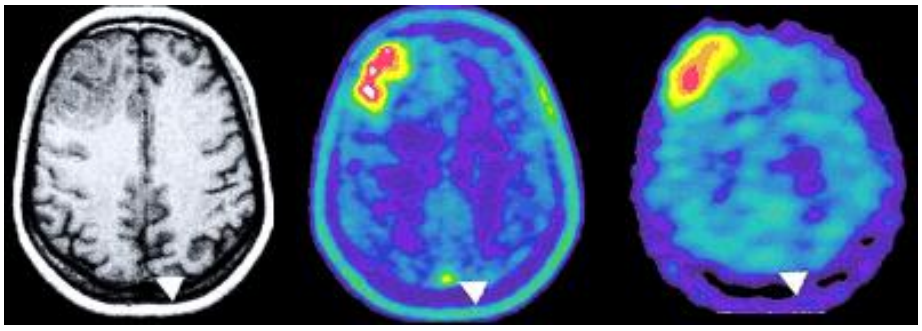
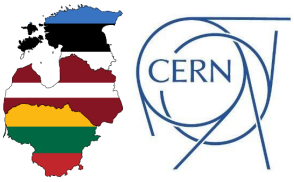


Figure 7. Comparison of diagnostic methods for brain tumor – oligodendroglioma

from left – magnetic resonance imaging (MRI), PET and SPECT scans

- radionuclides undergoing α or β^- decay can provide a therapeutic effect - with the radiopharmaceutical binding to cancerous cells, the decay products, respectively a helium nucleus or an electron with low energy, deposit their energy locally in the binding site of the radiopharmaceutical. With this, therapeutic nuclear medicine achieves similar effect like radiation therapy by affecting the DNA of cancerous cells, though, as the energies of α and β particles are low, the range



within tissue is short, therefore providing highly localized and confined 'irradiation' of cancerous cells with high linear energy transfer – relatively increased biological effect.

For a radionuclide to be considered for diagnostic nuclear medicine, apart from being nontoxic and chemically reactive to form bonds with the particular biological molecule, it must posess certain physical and chemical properties:

- half-life time of the decay corresponding to the time scale of the particular physiological process under investigation;
- biological half-life time should not be greater than the medical examination;
- decay channels limited only to one's for the specific diagnostic technique, meaning – radionuclides for SPECT should only have γ decay channels as the resulting annihilation radiation photons from β^+ decay would compromise the signal quality at the detector and vice versa – PET radionuclides should have extremely low probabilities of γ decays.
- generally free of α and β^- particle emissions, in order to reduce the radiation dose received by the patient during the medical imaging procedure;
- for SPECT radionuclides – suitable range of emitted photon energy, typically from 100 to 200 kiloelectronvolts.
- for PET radionuclides – preferably low energy of the emitted positrons, as higher energy positrons have an increased range before annihilation. Since PET technique detects the point of annihilation, while the point of interest is at positron emission, for longer range positrons the spatial quality of diagnostic information will be reduced due to blurring and distortions.

Similarly for a radionuclide to be considered for therapeutic nuclear medicine it must:

- an adequate half-life time for the decay, with the optimum being from 6 hours to 7 days – shorter half-life times reduce the flexibility of the delivery, while longer times increase radiation dose retained by the patient. Also the biological half-life time should be taken into account, which is the biological tracer molecule dependent.
- high probabilities of therapeutic type decay channels;
- adequate range of the emitted particle energy – high enough for cancerous cell size, while acceptably low for confinement of irradiated region;
- low abundance of decay products – 'daughter particles' – with long half-life.

For theranostic approach of nuclear medicine either radionuclides capable of decaying through both therapeutic particle and diagnostic gamma photon emission channels are considered or pairs of different isotopes for same chemical element with therapeutic and diagnostic decay channels are considered.

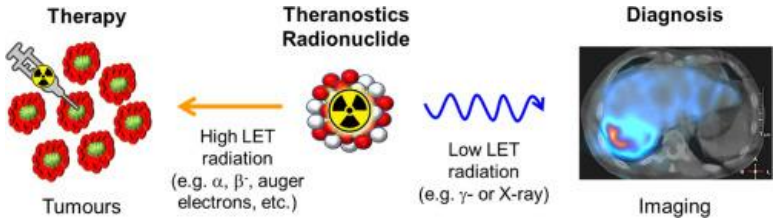


Figure 8. Schematic representation of theranostic radionuclide use

One of the most common methods of acquiring radionuclides for radiopharmaceutical production is the use of cyclotrons – specific type of a circular particle accelerator. Linear accelerator use for radionuclide production is not as wide spread, as one of the possible factors being lack of overall experience and knowledge in this field. Despite that, use of linear accelerators for radionuclide production provides certain advantages over the conventional cyclotron based production:

- linear accelerator use provides increased beam transmission with lowered beam losses;
- because of the beam losses, cyclotrons provide suboptimal α particle beams, which could be produced more efficiently with a linear accelerator achieving higher current and therefore production yields;
- cyclotrons generally do not feature beams of deuterons;
- linear accelerators provide a more stable operation characteristics and generally require less power.

Within the framework of the proposed facility, radioisotope production is considered by parallel use of the linear accelerator from synchrotron's injection line. As proposed within the NIMMS project collaboration, the use of linear accelerator would be be as a 'niche' – radioisotope production through nuclear reactions of targets that require either α particle or deuteron beams, therefore covering the production of radionuclides that is otherwise inefficient and sub-optimal with the use of cyclotrons. The design of the linear accelerator would thus be mainly tailored for energy range of α particles and deuterons necessary for radionuclide production and only secondarily – the correspondingly achievable proton beam energy and current range with the already established linear accelerator design parameters would be considered for radionuclide production through proton induced nuclear reactions. Study has been done within the NIMMS project[9] collaboration group to identify radionuclides that could be produced with the proposed linear accelerator design and could be considered for use in nuclear medicine, with the overview of proposed radionuclides and their main physical characteristics given in Table 1.

[9] Giovanni Bisoffi „**Options for medical isotope production with LINACs**",
at *NIMMS* project meeting 27.11.2020

Table 1. Radionuclides and their respective characteristics considered by *NIMMS* project for production with linear accelerator

Radionuclide	Usage of the radionuclide	Particle beam used for production	Necessary target material	Half-life time
Scandium-43	Diagnostic – PET	α	Calcium-40	3.9 h
Scandium-44	Diagnostic – PET	Deuteron	Calcium-44	4 h
Cobalt-57	Diagnostic – SPECT	α	Manganese-55	272 days
Copper-64	Theranostic (β^-)	Deuteron	Nickel-64	12.7 h
Copper-67	Theranostic (β^-)	α	Nickel-64	61.9 h
Indium-111	Diagnostic – SPECT	α	Silver-109	67.2 h
Tin-117m	Theranostic (β^-)	α	Cadmium-114 to Cadmium-116	14 days
Samarium-153	Theranostic (β^-)	α	Neodymium-150	2 days
Rhenium-186	Theranostic (β^-)	Deuteron	Tungsten-182 to Tungsten-183	90.6 h
Atastine-211	Therapeutic (α)	α	Bismuth-209	7.2 h

Tailoring the linear accelerator design for the afore mentioned radionuclide production, achievable energy and beam current in case of proton beams also allows the possibility of production of common, clinically already approved radionuclides for PET imaging – fluorine-18, oxygen-15, nitrogen-13 and carbon-11, either by proton or deuteron beams. In Table 2 are given the common nuclear reaction used for production of the mentioned PET isotopes either with proton or deuteron beams.

Table 2. Nuclear reactions used for production of common PET radionuclides

PET radionuclide	Nuclear reaction for production
Carbon-11	$^{14}\mathrm{N}(\mathrm{p},\alpha)^{11}\mathrm{C}$ $^{11}\mathrm{B}(\mathrm{p},\mathrm{n})^{11}\mathrm{C}$ $^{10}\mathrm{B}(\mathrm{d},\mathrm{n})^{11}\mathrm{C}$
Nitrogen-13	$^{12}\mathrm{C}(\mathrm{d},\mathrm{n})^{13}\mathrm{N}$ $^{16}\mathrm{O}(\mathrm{p},\alpha)^{13}\mathrm{N}$
Oxygen-15	$^{14}\mathrm{N}(\mathrm{d},\mathrm{n})^{15}\mathrm{O}$ $^{15}\mathrm{N}(\mathrm{p},\mathrm{n})^{15}\mathrm{O}$ $^{16}\mathrm{O}(\mathrm{p},\mathrm{d})^{15}\mathrm{O}$
Fluorine-18	$^{20}\mathrm{Ne}(\mathrm{d},\alpha)^{18}\mathrm{F}$ $^{18}\mathrm{O}(\mathrm{p},\mathrm{n})^{18}\mathrm{F}$ $^{16}\mathrm{O}(\,^{3}\mathrm{He},\mathrm{p})^{18}\mathrm{F}$

Thus the maximum α particle and deuteron beam energies provided by linear accelerator will be taken to provide maximum radionuclide production yield, which is dependent beam current and the reaction cross-section at the particular beam energy. With the radionuclide production proposed in Table 1., the linear accelerator design should operate with deuteron beams of maximum energies about 20 – 30 MeV and α particle beams with maximum energy of about 40 MeV.

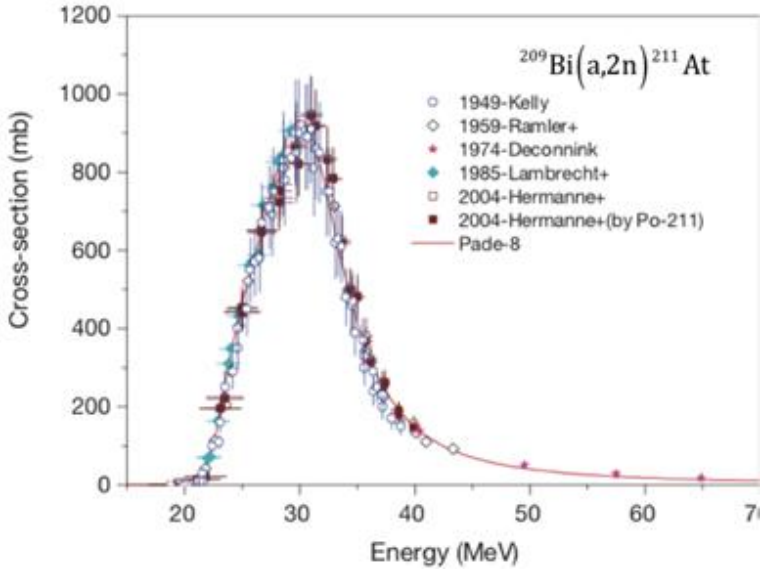


Figure 9. Reaction cross-section dependence on initial α particle beam energy for production astatine-211 from bismuth-209 target

Clinical gains of charged particle therapy

Every year in Europe more than 3.7 million new cancer cases are registered and also every year around 2 million deaths of oncological patients occur. Cancer treatment is an ever-evolving field having various technological advancements and innovations in all of the main branches of treatment – surgical procedures, chemotherapy and radiation therapy. Radiation therapy is indicated as a curative treatment option in more than 50 % cases of cancer patients around Europe. It should also be noted that in one out of four cases, where radiation therapy should be chosen as the curative treatment option, the patient is unable to receive this treatment with one of the main reasons being the limited availability of the necessary technologies – particle accelerators for medical use.

From a clinical point of view, use of helium and proton beams would provide the best clinical solution for paediatric tumors that require radiotherapeutical treatment. With advancements in pre-treatment imaging technologies providing information for more precise treatment volume delineation and overall increase of treatment plan complexity in conventional radiation therapy, the outcome of paediatric cancer treatment has improved a lot with the increase of overall survival rate. With the increase of survival rate in paediatric cancer treatment it becomes of uttermost importance to limit normal tissue exposure to ionizing radiation:

- in order to prevent late treatment related side effects. The rationale in paediatric radiation oncology is maximum sparing of normal tissue and critical organs as the dose constraints that are used for radiotherapy treatment planning in adults are generally not applicable for paediatric cases as radiobiological effects are different;
- as in paediatric cases the normal tissue and organs irradiated are still developing, exposure limitation is highly important to prevent growth and developmental defects.

Therefore, proton and helium therapy is ideal in paediatric brain tumors such medulloblastomas and gliomas, limiting radiation exposure to critical organs as eyes, ears and brain.

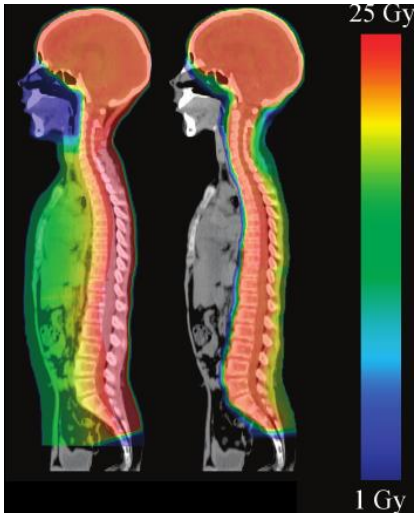


Figure 10. Comparison of dose distributions for paediatric medulloblastoma case, undergoing craniospinal irradiation procedure (*left* – high energy photons, *right* – protons)

While in treatment of sarcomas and lymphomas, radiation exposure is greatly reduced for heart, lungs and gastrointestinal system with the use charged particle beams compared to conventional therapy.

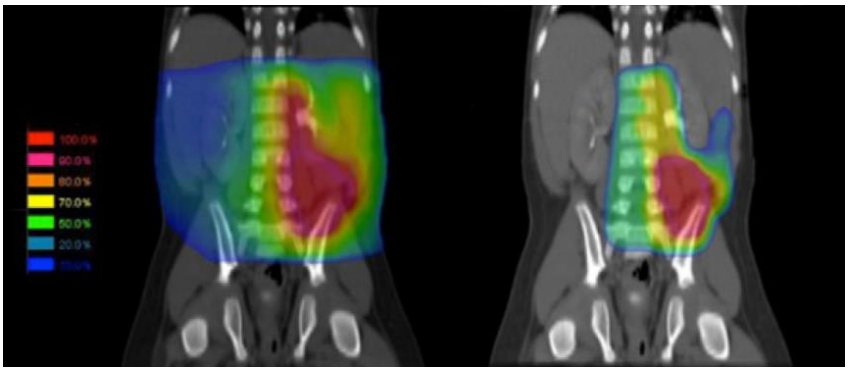


Figure 11. Comparison of dose distributions for paediatric pelvic sarcoma case (*left* – high energy photons, *right* – protons)

As already mentioned in the physical aspects of helium ion therapy – another crucial gain of helium ion therapy is the balance of conformality compared to protons with reduced nuclear fragmentation compared to carbon ions. With lesser nuclear fragmentation, biological uncertainties are decreased, improving estimation of treatment related toxicities, that is of high importance especially in pediatric patients. Moreover, helium ions produce lower neutron flux when interacting with matter than carbons ions and what is more – research studies suggest that the associated neutron biological dose for helium beams could be even lower than in proton beams.

Helium and proton beam therapy would also provide better clinical outcome and lowered normal tissue toxicities for tumors that are close to critical organs – mainly brain and head and neck (H&N) region tumors – and also allowing treatment of various central nervous system, eye, liver, lung, prostate, gynaecological and gastrointestinal cancer types.

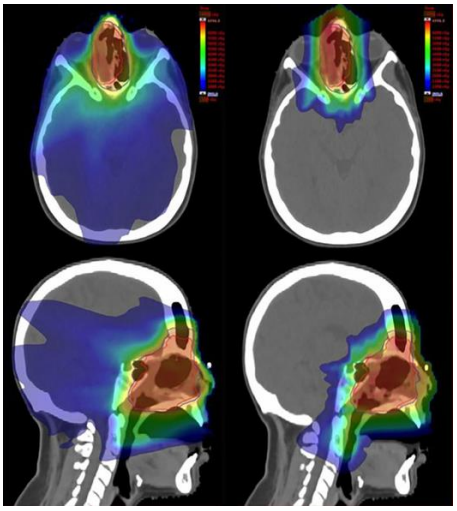
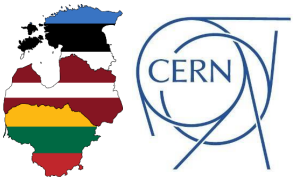


Figure 12. Comparison of dose distributions for nasopharyngeal tumor case (*left* – high energy photons, *right* – protons)



As mentioned in explanation on physical characteristics of helium-4 ions, these particle beams possess an increased linear energy transfer values compared to proton radiation, which therefore corresponds to higher relative biological effectiveness. While the biological effectiveness values of helium-4 ions do not quite reach the magnitude of carbon ions in order to fully overcome the radioresistance of hypoxic tumors (with low cellular oxygen content), clinical research is still underway for use of helium ions for such low oxygenated tumor types like glioblastoma, soft tissue sarcoma and others. On the other hand – the intermediate LET values of helium-4 ions correspond to relative biological effectiveness not reaching saturation (or even decrease) in the so-called “overkill effect”. For carbon ion beams at the end of their distal range LET values in certain cases and treatment geometries could reach a range that is too high to efficiently increase biological effect, resulting in cellular “overkill”. Range of helium-4 ion LET values is reasonably lower, therefore an increase of LET corresponds to an increase in RBE, no reaching cellular “overkill” region of biological effects.

Clinical possibilities within the nuclear medicine field

Diagnostic nuclear medicine provides unparalleled possibilities of functional imaging for radiation oncology compared to any other medical imaging modality. PET and SPECT imaging procedures allow far more precise delineation of the tumour volume, basing the delineation on functionality of cancerous cells as typical imaging modalities like computed tomography or magnetic resonance imaging could potentially 'miss' spatial extent of tumor volume in certain cases. Use of radiopharmaceuticals for diagnostic also allow the possibilities to identify functional regions within the tumor volume, therefore providing options for the so-called 'dose-painting' technique – adapting the dose distribution within the tumor volume and delivering higher doses to tumor regions with increased metabolism. 'Dose-painting' technique is still in the stage of it's 'clinical inception', but could provide increased local tumor control rates, thus increasing the overall clinical outcome of the treatment.

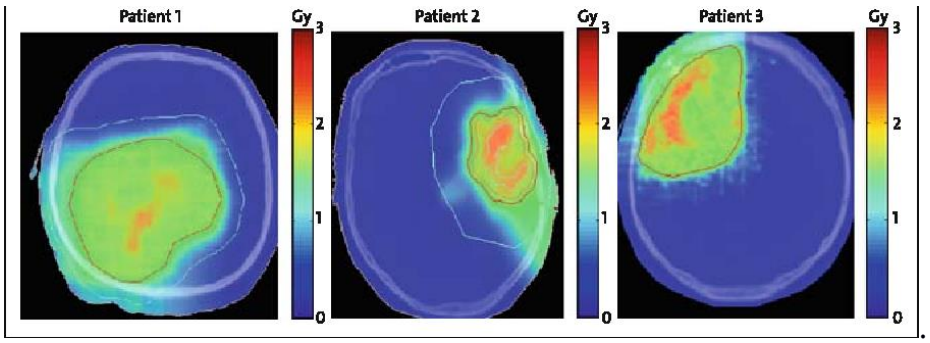


Figure 13. Dose distributions for proton based treatment plans of brain tumors, using the „dose painting" technique for non-uniform dose distributions

Functional imaging with radiopharmaceuticals could also provide important information on normal tissue and critical organ regions with increased functionality and metabolism, thus allowing pathways to include this functional information into radiation therapy treatment planning process to spare these regions of critical organs more with the aim of greatly reduced normal tissue toxicities. Moreover, nuclear medicine also has an important role in treatment response assessment, as SPECT or PET scans taken during the course of radiotherapy treatment would be able to provide information of both tumor and normal tissue response and provide crucial information if the treatment regimen should be adapted to increase tumor control or reduce normal tissue toxicities. In the same manner, SPECT or PET scans are taken regularly after the end of radiation therapy treatment course in order to assess treatment effectiveness, evaluate normal tissue response and provide information of possible reoccurrences of tumor.

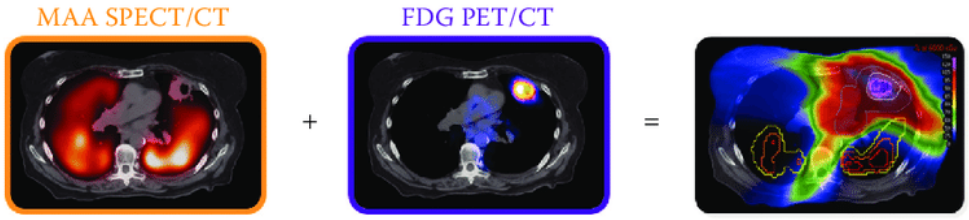


Figure 14. Schematic representation of functional lung avoidance technique for radiotherapeutical treatment: ^{99m}Tc-macroaggregated albumin SPECT data used for functional lung estimation, while fluorodeoxyglucose PET data are used for tumor volume delineation

Diagnostics within the nuclear medicine field are not limited just to radiation oncology as it is also an important diagnostic modality for the field of cardiology – assessing coronary artery disease, evaluating cardiomyopathy and for identification of possible heart damage during cancer treatment process.

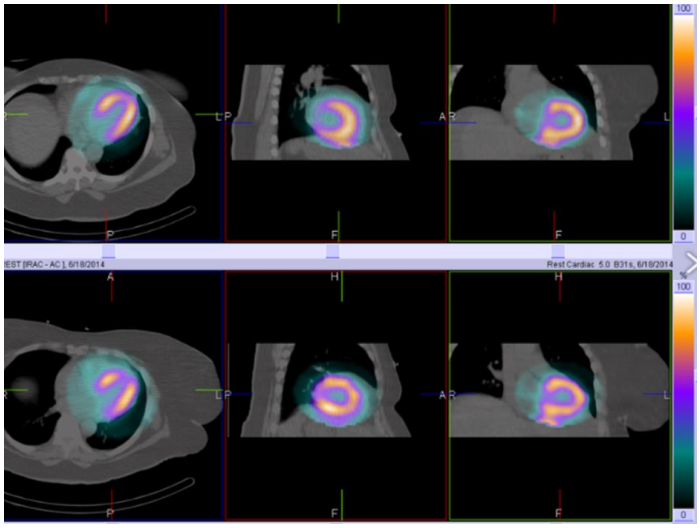
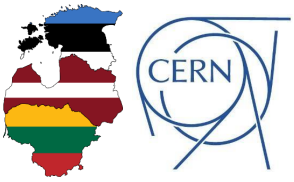


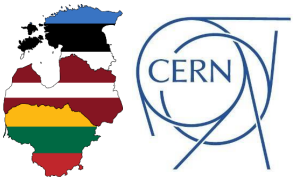
Figure 15. SPECT and computed tomography image fusion for cardiac function assessment during stress conditions

As for therapeutic capabilities within the nuclear medicine field, therapeutic radionuclides are mainly considered in treatment of 'spread-out' cancer types such as lymphomas and leukaemias, bone metastases, limited size solid tumors and spread of micrometastatic cancerous cells. The main advantage of targeted radionuclide therapy comes from energy deposition characteristics of radionuclides used within radiopharmaceuticals – the emitted α or β^- particles have relatively low energy which corresponds to a short range of particles within tissue, therefore dose deposition is confined to treatment site limiting normal tissue exposure to the particulate radiation. Considering α particle emitting radionuclides for treatment another advantage comes from high values of linear energy transfer for such low energy level range that corresponds to maximum radiobiological effect at cancerous cells. Astatine-211, which is considered as of the radionuclides for production with the proposed linear accelerator design of this facility, is considered as one of the most promising options for targeted α particle therapy.



A novel and evolving field in nuclear medicine is theranostics or so called 'treat what you see' approach – using radionuclides or radionuclide pairs in radiopharmaceuticals that decay in both diagnostically and therapeutically usable modes. Therefore theranostics concomitantly provides diagnostic information about the spatial location of cancerous cells, while delivering therapeutic effect from β^- or α particle emissions. Theranostics also provides pathways for delivered dose quantification in nuclear medicine, providing pathways for more personalized treatment, treatment associated risk estimation and input data for radiobiological studies of radionuclide therapy. By the proposed design of facility's linear accelerator, numerous radionuclides applicable for theranostics could be produced such as copper-64 and the clinically approved radionuclide copper-67, tin-117m radionuclide, which also currently in clinical test phase for artery plaque treatment, clinically approved samarium-153 for pain palliation and rhenium-186 for pain palliation in skeletal bone metastases.

Overall, clinically nuclear medicine in Advanced Particle Therapy center in Baltic states could provide pathways for elevated charged particle therapy treatment workflow, providing the possibilities of functional imaging for tumor volume delineation and tumor therapeutic response assessment during and after the radiotherapy course. Moreover, additional diagnostic, therapeutic and theranostic capabilities within the facility would be provided for various oncological and non-oncological conditions.



The overall conceptual technical design

Central part of the proposed Advanced Particle Therapy center is the helium synchrotron – a completely novel particle accelerator technology proposed by scientists at CERN working within NIMMS (Next Ion Medical Machine Study) collaboration project. Helium synchrotron would be a completely novel particle therapy system – „first of the kind" – expanding the clinical possibilities compared to protons, while reducing the dimensions and technological complexity that is necessary for a carbon ion therapy facility. Helium synchrotron conceptual design is currently in an active development stage with the concept design ready in summer of 2022, that would be followed by a technical design development in 2022 and 2023, that can be done with contributions from CERN Baltic Group scientific institutions.

As already stressed, helium synchrotron is a design developed by CERN, therefore CERN is one of the most crucial partners in delivering the proposed Advanced Particle Therapy center of Baltic States. CERN already has an extensive experience in developing the design of particle therapy treatment center designs, as before the NIMMS collaboration, the CERN based collaboration project PIMMS (Proton-Ion Medical Machine Study) developed the necessary technologies of particle therapy machines that were adopted in design and construction of two particle therapy centers in Europe: MedAustron (Austria) and CNAO (Italy).

The overall design of infrastructure for Advanced Particle Therapy center in Baltic States can be divided in these main technological blocks:

- **high radiofrequency linear accelerator** 'serving' two main purposes: particle 'pre-acceleration' for injection into synchrotron and option of parallel production of radioactive isotopes, mainly with α-particle (helium) beam, for use in nuclear medicine. Linear accelerator design is planned as multi stage, providing different injection energies for different particle types.
- **ion sources**, providing protons and helium-4 ions. For research purposes, an ion source providing helium-3 ions could be installed as well. In later stages of the center an additional ion source of fully stripped carbon ions could be installed for research purposes.
- **helium synchrotron** for acceleration of helium and proton particle beams for radiation therapy treatment. The proposed synchrotron design would be able to reach maximum beam energy of 220 MeV per nucleon for helium-4 ions, which corresponds to treatment range of about 30 centimetres. The proposed design of helium synchrotron could run either on 1.65 or 2 Tesla magnets, having a beam rigidity around 4.6 Tm. Such a synchrotron design provides the possibility to accelerate all ion beams with charge-to-mass ratio 1:2 up to 220 MeV per nucleon. Thus, in the future development of the center, if carbon ion source would be installed, it would be possible to provide a carbon beam for research purposes, having a range up to about 11 centimetres. As this range does not provide sufficient range for medical treatment, the carbon ion beam could be used for various medical physics and pre-clinical research studies. As for proton beams, 220 MeV energy per nucleon provides the same treatment range in water as for helium-4 ions, but since protons have a charge-to-mass ratio 1:1, the proposed syn-

chrotron design could provide maximum proton beam energy up to about 700 MeV that could be used for research purposed in material sciences.

- **two beamlines for treatment** rooms: one of the treatment rooms would have a fixed, static horizontal beam line, while the other treatment room would be equipped with a rotating gantry system. Treatment beamlines would be equipped with nozzles capable of delivering both passive beam scattering techniques and also having scanning magnet system for a pencil-beam scanning technique.
- **one beamline for research** usable for various research studies in the fields of radiation oncology and corresponding pre-clinical research, radiobiology and biophysics, medical physics, material sciences and others.
- **target system for radioisotope production** consisting of all the metallic, gaseous or liquid targets necessary for the considered radionuclide production.

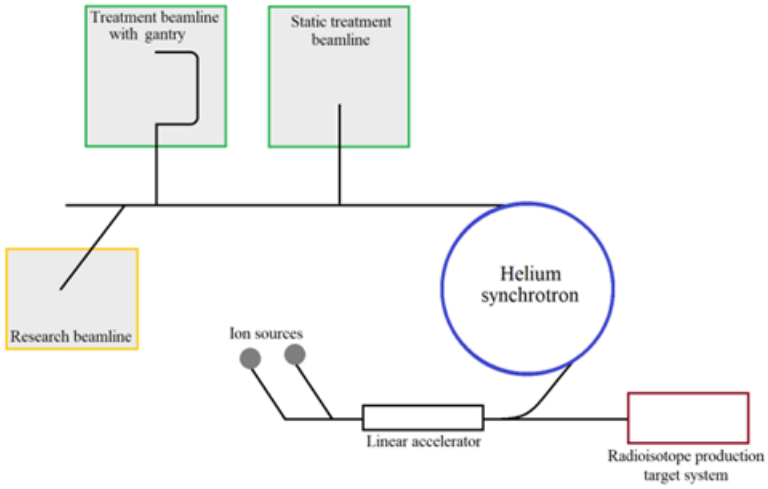


Figure 16. Schematic representation of the overall technical design of the proposed facility

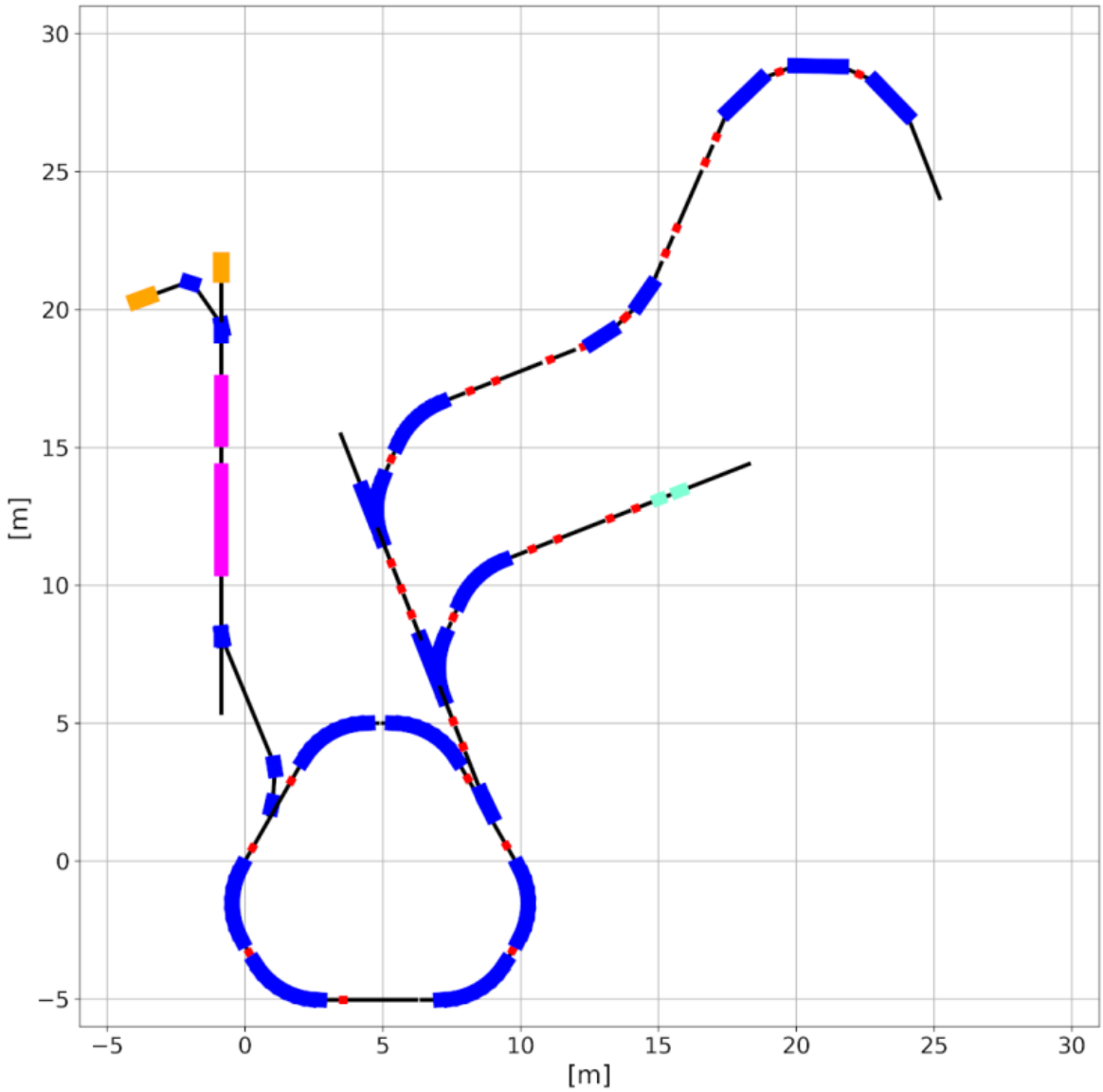


Figure 17. Scaled layout of the proposed accelerator complex lattice design[10]

[10] Design created by **Mariusz Sapinski (GSI/SEEIIST)** with Maurizio Vretenar (CERN) and Elena Benedetto (SEEIIST/CERN)

Particle accelerator technologies. New innovations and industry involvement

The technical design of Advanced Particle Therapy Center in Baltic States would be done in close collaboration with CERN, particularly the NIMMS project group. The helium synchrotron design proposed by the NIMMS project group would be the 'heart' of this facility, while also building on other established technological advancements within the project collaboration. Therefore the novel design of the facility would come with various advancements in the field of medical accelerators and corresponding technology such as:

- multiple particle operation;
- multi-energy particle beam injection and extraction;
- slow extraction methods;
- faster dose delivery with higher intensity of the beam;
- greatly increased extraction rates for very high dose rate, so-called, *FLASH*, therapy;
- gantry system for beam delivery;
- novel linear accelerator design that provides parallel radioisotope production capabilities;
- novel bending magnet and beam optics design for a helium synchrotron system, providing a compact accelerator complex with simple lattice design.

As in regards to technical considerations for the design of Advanced Particle Therapy center in Baltic States, it should be noted, why the particular choice of overall design for the facility. As discussed with CERN representatives together with CERN Baltic Group on October of 2021, five particle accelerator designs at the heart of the facility were proposed, with the comparison metrics given in Figure 17.

increasing cost →

	Cyclinac	C-linac	He-synchrotron	C-synchrotron (RT)	C-synchrotron (SC)
Particles	p	p, He, C	p, He	p, He, O, C	p, He, C
Dimensions (1)	~400 m² (?)	~600 m²	~600 m²	~1,200 m²	~600 m²
Approx. cost (2)	20	30	20	40	30
R&D needed	medium	high	low	low	high
Risk for R&D	low	medium	low	low	medium
Time to TDR (3)	~1y	~4y	~1.5y	~1.5y	~5y
Radioisotopes	Yes, wide range	no	if needed	yes	if needed
Gantry (4)	no	no	yes (>5y)	yes (>5y)	yes (>5y)
Comm. interest	low	medium	medium	low	high

Note that all these options will need medical licensing before treating patients (cost and time)

(1) Accelerator only – no rooms, without shielding
(2) Accelerator only. Rough estimate in arbitrary units for cost of acc. components
(3) Assuming an expert team working full time; TDR=Technical Design Report
(4) Use of SIGRUM superconducting gantry

Figure 18. Particle accelerator design option comparison for Advanced Particle Therapy center in Baltic States[11]

[11] Maurizio Vretenar „**Accelerator technology and advanced particle therapy options for Baltics**", February 7th, 2022 at Baltic Assembly and CERN Baltic Group meeting

Helium synchrotron design was chosen for the proposed facility as this particle accelerator design cost is comparable to commercially used particle therapy machine options and with a lower associated R&D risk, while providing options for immediate treatment options with proton beams, new treatment modality possibilities, such as *FLASH*, and engaging Baltic State industries for the production of the accelerator and connecting Baltic States with an on-going cancer research projects and programmes throughout the Europe. Proposed particle accelerator system is also reliable as generally use of proven technologies will be used in the design, that can be found in the design and construction of main hadron therapy particle accelerators within Europe and within particle physics accelerator complex of CERN.

As mentioned in other paragraphs – helium synchrotron design is a complete novelty, with first design results to be presented[12] at 13th International Particle Accelerator conference this year (2022), also with contributions from Baltic States scientists. The following paragraphs are largely based on these design results and considerations of NIMMS Helium synchrotron design working group.

Helium synchrotron design is rather compact compared to other medical particle accelerator designs and would use generally established particle accelerator concepts, therefore posing minimized risk of associated R&D risk, when delivering the facility. Initially and currently proposed schematic design of helium synchrotron is given in Figure 18. The initial design was optimized to be relatively simple, with having 4 dipole magnets of 90 degrees. As the necessary dipoles of 90 degree bend in the magnetic system are rather large in dimensions and challenging, if superconductivity approaches for carbon ions in the future are considered, more efficient synchrotron lattice design comes in a triangular-like shape. Triangular lattice design is the currently proposed baseline design for helium synchrotron, consisting of 6 dipole magnets of 60 degree bend and 3 “straight sections” – one for injection, one for extraction and one for the accelerating radiofrequency cavity, along with the necessary quadrupole, sextupole and corrector magnets and septum magnets for injection and extraction. Dipole magnets proposed in the design are to be constructed with edge focusing in order to achieve more favourable beam optics performance, lowering the number of necessary quadrupoles in lattice design. The maximum acceleration energy of helium-4 ions in the proposed design is 220 MeV per nucleon, which corresponds to magnetic rigidity of 4.5 Tesla * meters. The dipole magnet strength for the initial design is considered at 1.65 Tesla. Moreover, the triangular lattice layout of 3 straight sections and 3 magnet sections provides a modular approach for future upgrades – by magnetic system exchange to superconducting version of magnetic flux density (field strength) of 2.4 Tesla, the proposed accelerator complex could be used for carbon ion acceleration up to energies relevant to achieve necessary treatment ranges.

[12] Paper in preparation for IPAC22: **M. Vretenar**, E. Benedetto, M. Sapinski, M. E. Angoletta, G. Bisoffi, J. Borburgh, L. Bottura, K. Paļskis, R. Taylor, G. Tranquille: *A Compact Synchrotron for Advanced Cancer Therapy with Helium and Proton Beams*

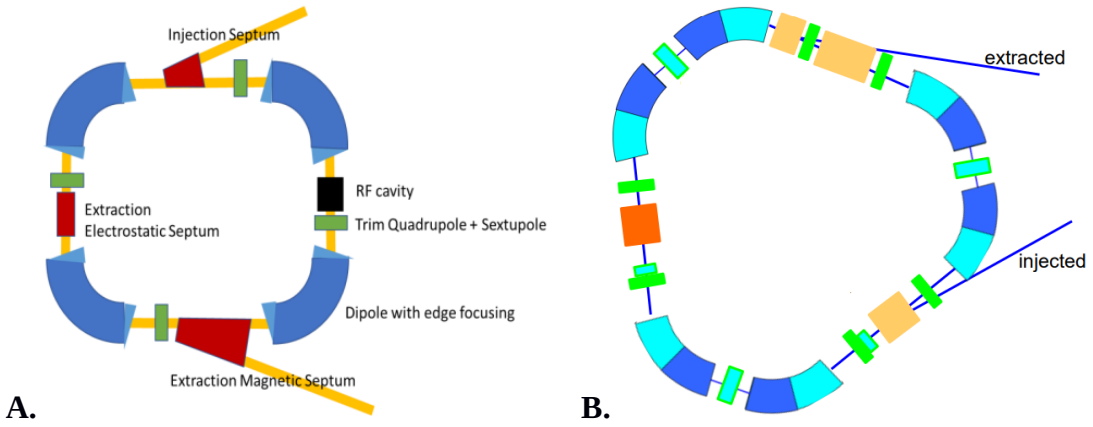


Figure 19. Initially proposed helium synchrotron lattice square-like design (**A)** and current baseline design with triangular-like lattice design (**B)** [13]

Although the full helium synchrotron machine technical design is still in development, aspects of the used ion sources and linear accelerator for injection are already considered. As for the ion sources, two options can be considered – electron-beam ion sources (EBIS) or electron-cyclotron resonance sources (ECRIS). Use of electron-beam ion sources is preferable as they provide beams with greatly decreased beam emittance and generate more pure beams compared to electron-cyclotron resonance sources – lower pressure in EBIS source generates less impurities, therefore decreasing problems associated with the initial accelerator tune accelerating all the ions of charge-to-mass ratio of 1:2. The main downside of EBIS type ion sources is a lower produced beam current – although multi-turn injection is possible, it becomes challenging at low ion source beam currents, but generally feasible at intensities considered for therapy. Beam current that is estimated for typical treatment geometry and dose level is on the order of 2 miliamperes. Such a beam current is feasible with modern ECRIS type ion sources, such as AISHA from INFN/LNS or PK-ISIS from Pantechnik, that is also able to deliver carbon ion beam current of about 50 microamperes, usable for research-driven purposes.

As for the injector system, a system of linear accelerators will be used. The proposed injection energies are 10 MeV per nucleon for protons and 5 MeV per nucleon for helium-4 ions, with the possibilities of going even lower injection energy of 3 MeV per nucleon for helium-4 ions in consideration of on-going research. As two different injection energies are to be considered in the design, linear accelerator system design is currently proposed with two stages – radiofrequency quadrupole with drift tube linear accelerator, that is mainly designed for particles with a charge to mass ratio of ½ (like helium-4 and carbon-12) to an injection energy of 5 MeV/u, while the second section would be another drift tube linear accelerator, designed for particles with a charge to mass ratio of 1 – protons – and delivering injection energy of 10 MeV.

Beam parameter monitoring system, while still in development stage, has reached an outline design considerations at the current stage. As compact synchrotron design poses spatial constraints, only the most essential beam diagnostics are to be done in the proposed synchrotron design – beam intensity, beam position and profile and lastly – tune. Diagnostic

[13] Lattice designs and schematics created by **Elena Benedetto (SEEIIST/CERN)**

measurement systems are to be kept of relatively simple designs, while also respecting spatial requirements.

The proposed injector linear accelerator system design will be generally based on the design of CERN accelerator complex injector „LINAC4" using radiofrequency (RF) power at frequency of 352.2 MHz, although design studies for linear accelerator running at frequency of 750 MHz are still under-way in NIMMS collaboration as such working frequency would greatly reduce dimensions of the injector. The linear accelerator proposed would also be multi-stage, allowing energy extraction levels both for injection into synchrotron and use for radioisotope production system.

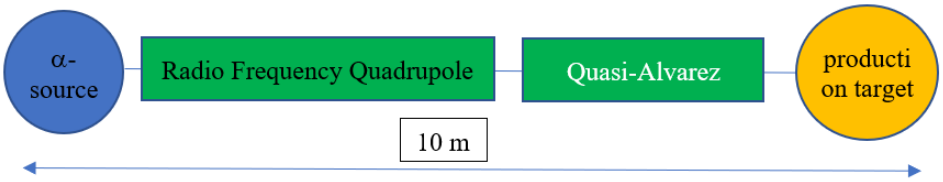


Figure 20. Schematic representation of the linear accelerator initial design for parallel production of radionuclides[14]

The rotating beam delivery system with a gantry for one of the treatment rooms would be done based on the mechanical support structure design proposed within the NIMMS collaboration by the *HITRIplus* project mechanical design team. Moreover, a very notable part of *HITRIplus* mechanical design team consists of scientific personnel from institutions of CERN Baltic Group. The proposed gantry mechanical support structure within the scope of NIMMS and *HITRIplus* projects is considered with superconducting magnet system for delivery of carbon ion therapy beams. The same mechanical structure design could be used for the proposed Advanced Particle Therapy center in Baltic states just using low field superconducting magnet system with magnetic flux density (field strength) of 2.8 Tesla as helium-4 ions require lesser magnetic field strength to achieve the same bending radius compared to carbon ions, which require in 4 Tesla magnetic system in current *HITRIplus* design.

[14] Giovanni Bisoffi „**Options for medical isotope production with LINACs**",
at *NIMMS* project meeting 27.11.2020

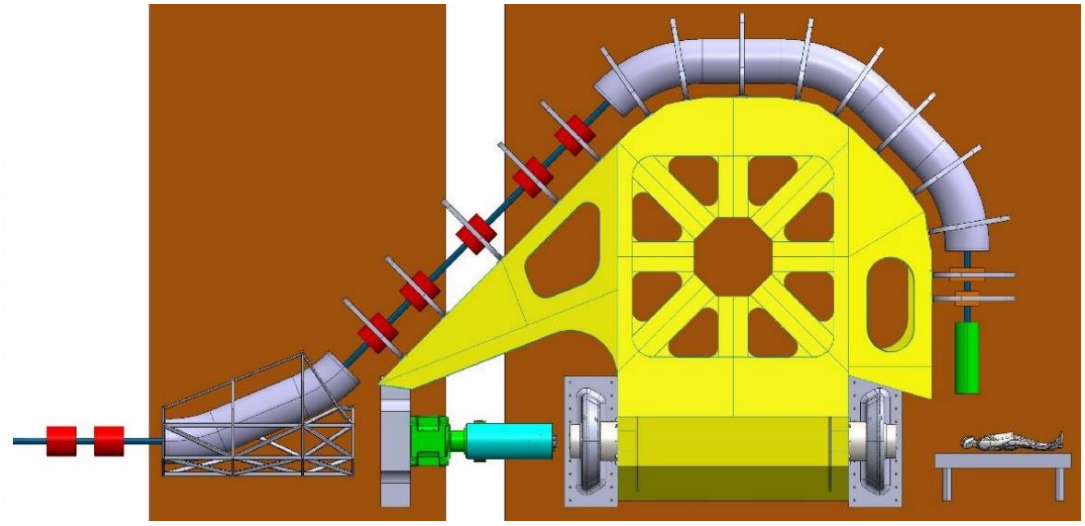
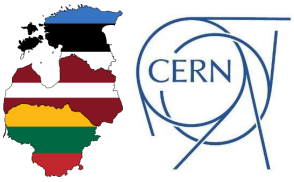


Figure 21. Representation of the initial design proposal of a rotating gantry beam delivery system[15]

With all the afore-mentioned details, the proposed facility would be the first in Baltic States to have an extensive particle accelerator system, that could foster an environment for innovations of particle accelerator and corresponding support system technologies, facilitate research and academic studies in accelerator physics and technologies within the Baltic States and provide pathways for Baltic States industrial involvement in producing particle accelerator components and support systems, such as radiofrequency cavities, dipole and quadrupole magnets, cooling systems and mechanical structures of the gantry. It should be also noted, that the results of the on-going work by Baltic States researchers at CERN regarding additive manufacturing methods for accelerator component production could also be used in the technical delivery of the proposed accelerator complex, particularly in production of radiofrequency cavities and radiofrequency quadrupole section of the linear acceleration system.

[15] Piacentini, L. **Project Development of a Rotating Transferring Line for Carbon Ions Used for Medical Scope**, Unpublished work, 26.03.2021 – from *NIMMS* project meeting 25.02.2022



Current innovation trends in hadron therapy accelerators. Novel technology research and development possibilities

Novel hadron therapy treatment approaches are opening necessities for completely novel technology development and integration within hadron therapy accelerator complexes. This chapter is to identify these open windows in hadron therapy accelerator technologies and needs for possible innovations regarding novel technology additions, based on the ideas mentioned in a recent study[16] on status of helium ion therapy and future trends. Technological advancement possibilities provide grounds for research and innovations in engineering solutions and technologies that could be developed in the future within the facility provided the proposed infrastructure.

Magnetic resonance imaging (MRI) system integration: use of MRI for imaging the patient in the treatment position would provide unparalleled soft-tissue contrast in the images and allow non-ionizing imaging for monitoring during beam delivery, opening options for adaptive therapy approaches. MRI integration within conventional electron accelerators has already found a way into clinical workflow, while for particle therapy, this is still in the early development stages, mainly due to physical complexities of charged particle interactions with magnetic imaging fields. Technical integration strategies and physical modelling is of interest for such novel systems, as especially for technical integration shielding and component construction aspects must be thoroughly considered, to avoid the mutually deteriorating effects between the accelerator and MRI systems.

Technical necessities of *FLASH* delivery: biological studies have shown that in order to achieve the normal tissue sparing *FLASH* effect, doses on the order of 8 – 10 Grays must be delivered with a dose rate larger than 50 – 100 Grays per second. As this poses a rather complex challenge from accelerator technology perspective due to space charge imposed limits and technological capabilities of magnets for pencil beam scanning systems, mainly switching speeds, there is a wide array of options of innovation and technology optimization within this field regarding single-turn multiple energy extraction, slow extraction with radiofrequency knock-out, three-dimensional range modulators technology and others. Another important aspect regarding *FLASH* delivery is beam instrumentation and detection system development, that can give measurement quality and reliability necessary for dose delivery rates applicable to *FLASH* therapy.

Hadron therapy arc delivery: while from clinical stand point results acquired by treatment plan modelling show a clear improvement with sparing of normal tissues and organs at risk (OARs) using arc delivery, it poses very high level of technological complexity necessary for such a delivery. Technological combination of precise mechanical rotational motion of the gantry synchronized with continuous spot-like irradiation poses significant challenges for a proper control mechanism system considering both the necessary beam energy and rotation angle dependent settings of beamline elements and control signals for scanning magnets. Therefore dedicated solutions for control system elements and technologies must be

[16] Mairani A, Mein S, Blakely EA, Debus J, Durante M, Ferrari A, Fuchs H, Georg D, Grosshans DR, Guan F, Haberer T, Harrabi SB, Horst F, Inaniwa T, Karger CP, Mohan R, Paganetti H, Parodi K, Sala PR, Schuy C, Tessonnier T, Titt U, Weber U. "**Roadmap: helium ion therapy**", *Phys Med Biol*., 8. Apr 2022, doi: 10.1088/1361-6560/ac65d3

developed. As control systems, also proper beam instrumentation and feedback systems should be developed for arc delivery techniques that could provide data for log-based quality assurance for each of the patients, improving the reliability and lowering risks of the treatment process.

What should be noted from the clinical point of view – helium ions could provide the best efficacy in arc delivery in terms of physical dose distributions, as slight advantages could be gained over carbon ions as the overlapping carbon ion fragmentation tails could create elevated dose regions outside the treatment volume.

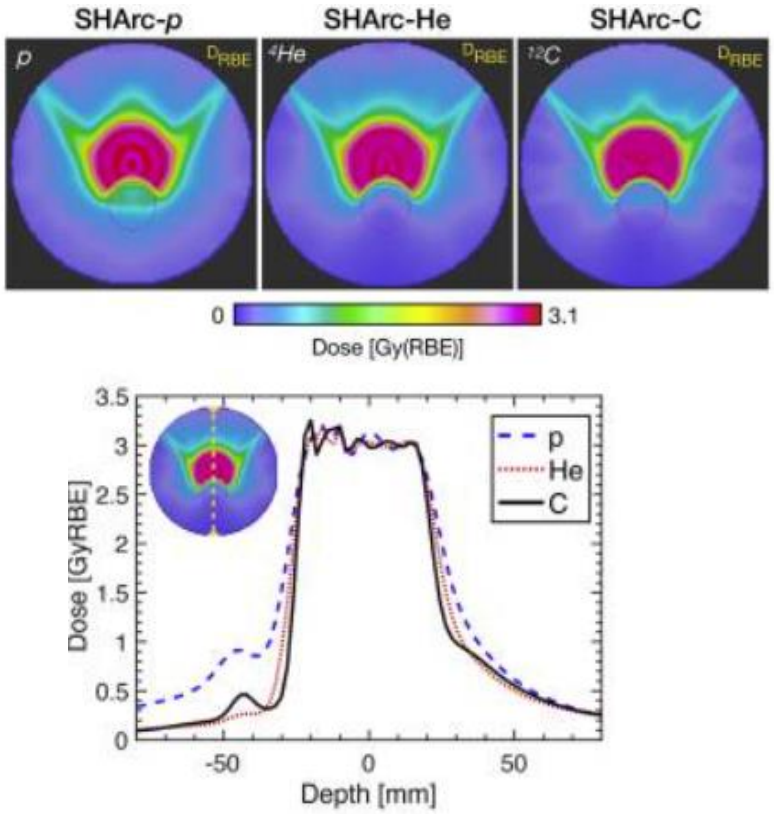


Figure 22. Simulated dose distributions for arc delivery with spot-scanning hadron arc (SHArc) approach developed at HIT (*upper*, *from left* – protons, helium and carbon ions) and corresponding central axis dose profile (*lower*)[17]

Transmission and in-vivo imaging systems:

Helium ions usage in clinical environment is also considered for ion radiographical purposes – acquiring pre-treatment or treatment verification images. For ion radiography high energy helium ions are used, providing full transmission through the body of the interest. Based on the physical scattering properties, helium ion radiography images can provide superior spatial resolution compared to protons, while keeping the imaging dose on the same order. Compared to heavier particles like carbon, for ion radiography purposes helium ions achieve the lowest imaging dose, and based on the relative independence of calculated stopping power

[17] Mein S, Tessonnier T, Kopp B, et al. Spot-Scanning **Hadron Arc (SHArc) Therapy: A Study With Light and Heavy Ions**. *Adv Radiat Oncol.* 2021;6(3):100661. Published 2021 Feb 4. doi:10.1016/j.adro.2021.100661

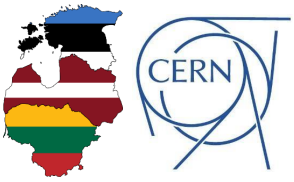
values of imaged tissue – helium ion imaging could become the main option at multi-particle synchrotron-based facilities. Although ion radiography detectors proposed for proton beams could be of use for helium ion imaging, it would be highly beneficial to tailor the imaging detector design specifically for helium to maximize the performance. Because of helium ion nuclear fragmentation, signal filtering systems should be developed to "disentangle" the acquired information as the usable one originating from primary particles and secondary fragment related background signal. Construction of a helium ion tailored imaging detector and choice of materials should also be researched and developed in order to minimize secondary nuclear fragment emission.

An important, emerging subject of interest within hadron therapy is the so-called in-vivo imaging or range verification – methods to verify beam or Bragg peak position within the patient body. The main two proposed technologies for that are:

- positron emission tomography (PET) approach: with nuclear reaction processes, beta(+) emitting isotope particles are produced, which emit positrons, that annihilating with electrons, produce two anti-parallel gamma photons that are then detected by the PET system;
- prompt gamma detection approach: gamma photons that are emitted by fast de-excitation of the nuclei after nuclear reactions are detected by specialized detectors, placed at optimized positions for detection.

Helium ions pose challenges in PET approach as the acquired activity is lower per given dose to reduced particle fluence, activity distribution correlation with range of primary particles is more complex because of long range secondary particles and generally there the activity "peak" around the Bragg peak is less pronounced as with proton beams. Such challenges also appear for prompt gamma approaches for in-vivo imaging of helium ion therapy process, as clear parameters of signal intensity per dose, secondary particle background signal and accurate nuclear reaction physics models are yet to be defined and improved. From a technological perspective of respective detector construction, questions regarding decreased signal counts compared to proton beams should be addressed. Currently, in research and development stages are novel detector technologies able to detect and distinguish both positron-electron annihilation photons and prompt gamma photons from nuclear de-excitations. Technical integration of PET detector systems within the treatment complex are also of huge interest for the future, as PET detector close to beamline could allow "real-time" PET imaging, allowing detection annihilation event signals coming from produced radioactive isotopes with a life time in the range of miliseconds. Also, completely novel detector approaches for helium ion beams could be developed, as helium ions produce wider array of secondary particles compared protons. One such pathway is under investigation at CNAO (Italy) using a specifically developed detector system for secondary proton detection from heavy particle beams.

Another in-vivo imaging technique is the detection of ionacoustic sound waves produced by Bragg peak energy deposition. As compared to protons, helium ion beams provide more localized energy deposition at Bragg peak and with increased energy loss intensity - the thermoaccoustic signal emmited could be greatly enhanced. Based on this, novel ionacoustic detectors and signal processing methods could be developed specific for helium ion therapy.



The proposed research directions of the facility

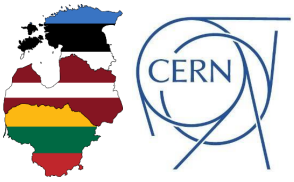
Considering the proposed infrastructure of the facility and a dedicated research beamline, scientific research stands as another main function of the proposed Advanced Particle Therapy center in Baltic States. With the proposed infrastructure of the facility the main research areas would be in the fields of accelerator physics, accelerator technology, medical and biophysics, radiation oncology pre-clinical research and clinical trials, nuclear medicine, material sciences, radiochemistry and others. As a scientific research institution Advanced Particle Therapy center in Baltic States would provide collaborations with universities of Baltic States and other international partners allowing 'beam time' on the dedicated research beamline for specific research projects. Some outlooks on main scientific research activities and direction possibilities are given in the following paragraphs, mainly linked to the clinical functionality of the facility.

Scientific research activities of the center would also be closely linked to the clinical functions of the facility as many of the proposed fields of study could provide results for more effective and novel radiation therapy treatment options. Radiation oncology research activities would mainly focus on:

- necessary helium ion therapy pre-clinical research and clinical trials in order to move into full scale clinical operation with this modality for cancer treatment;
- novel radiopharmaceutical design, production and necessary pre-clinical research and clinical trials using diagnostic, therapeutical and theranostic radionuclides proposed for production with facility's linear accelerator design;
- as the proposed facility's synchrotron design would allow the possibility of very high dose rate delivery up to 100 grays per second, the facility would take part in the pre-clinical research and associated clinical trials for so-called *FLASH* therapy;
- in the future, adding the additional carbon ion research beamline possibility, pre-clinical research for carbon ion therapy could be carried out along with studies of carbon ion effectiveness in treatment of hypoxic cancer cell lines;

Corresponding to the clinical activities, medical physics and biophysics research activities would be mainly dedicated to:

- dose deposition characterization and biological effect estimation for advancement of treatment planning system calculation algorithms in terms of the effects of projectile fragmentation, target fragmentation, microdosimetrical quantity estimation and biological effect modelling for helium ion therapy;
- with the additional future research beamline of carbon ions, physics research would be mainly aimed at projectile and target fragmentation and biological effect modelling in mixed particle beam with the aim to lower treatment planning associated biological effect modelling uncertainties;
- studies of linear energy transfer parameter inclusion in radiotherapy treatment plan optimization could be performed, carrying out also the corresponding clinical research activities;
- studies on very high dose rate treatment options, the so-called *FLASH* therapy – biological effect estimation, physical and biological modelling studies with the



goal of *FLASH* effect inclusion in treatment planning system calculation algorithms;

- studies on *in vivo* dosimetry – treatment beam position assessment within the patient through use of positron emission tomography of radioactive element production in patient's body after treatment or prompt gamma photon registration;
- studies of proton and/or helium ion radiography in order to produce tomographical images for treatment planning with lowered associated range uncertainties;
- in the field of nuclear medicine – studies on modelling novel radiopharmaceutical pharmokinetics and associated patient specific dosimetry for better modelling of treatment related side effects and overall radiobiological effectiveness.

Closely linked with scientific research activities for nuclear medicine would be the aspect of radionuclide production, associated with the fields of material sciences, nuclear physics and radiochemisty – studies on novel target systems for nuclear medicine, measurements for corresponding nuclear reaction cross-sections for production yield calculation and studies on radiochemical purification methods for the produced radionuclides.

It must be noted, that the main proposed research possibility pathways are also in close correspondence with necessities identified in a recent study[18] regarding clinical status of helium ion therapeutical use. Thus, with the proposed research directions, results of high relevance within hadron therapy scientific community could be achieved, facilitating international scientific cooperations.

[18] Mairani A, Mein S, Blakely EA, Debus J, Durante M, Ferrari A, Fuchs H, Georg D, Grosshans DR, Guan F, Haberer T, Harrabi SB, Horst F, Inaniwa T, Karger CP, Mohan R, Paganetti H, Parodi K, Sala PR, Schuy C, Tessonnier T, Titt U, Weber U. "**Roadmap: helium ion therapy**", *Phys Med Biol*., 8. Apr 2022, doi: 10.1088/1361-6560/ac65d3