Review of the collaboration's "R&D proposal for the preliminary and pre-construction phases"

Feedback

The Laser-hybrid Accelerator for Radiobiological Applications (LhARA) formed the basis of the STFC proposal to the UKRI Infrastructure Advisory Committee to establish the Ion Therapy Research Facility (ITRF). This document presents the feedback from the review of the LhARA collaboration's proposal for a five-year programme of R&D that is designed to be carried out during the Preliminary Activity and Preconstruction phases of the development of the ITRF. A page on the LhARA collaboration's wiki has been prepared to record the terms of reference, review panel, documentation, presentations, and feed back.

The review was carried out between August and October 2022, with formal meetings held on the 30th August[1] and the 26th and 27th October. The review panel was presented with a top-level description of the LhARA initiative and the LhARA project on the 30th August. A more detailed review of the radiation biology programme took place on the 26th October. The accelerator-science aspects of the LhARA project was carried out on the 27th October. The accelerator-science review focused principally on the two-years of the programme proposed for the Preliminary Activity.

Review panel

International Advisory Board of the Centre for the Clinical Application of Particles:

- Mile Lamont (CERN) (Chair);
- Michael Baumann (DKFZ);
- Paul Bolton (LMU); and
- Brita Singers Sørensen (Aarhus)

Expert reviewers:

- Gianluigi Arduini (CERN)
- Christian Carli (CERN)
- Malek Haj-Tahar (PSI)

1. Review of radiobiology input for LHARA

Brita Singers Sørensen

Quality of the science and technology:

The radiobiology program encompasses a panel of the currently hot topics both within radiobiology as such, and more specifically within particle radiobiology. The research areas are focusing on tumor radiobiology as well as on radiation modalities which can potential spare normal tissue.

[1] This link is to an Indico page for which the pass phrase is CCAP3008.

One main area here within is impact of LET on cellular pathways, such as DNA repair, the combination with inhibitors of different pathways, and gene knockdown systems. Factors, such as hypoxia, which is known from photon clinic to highly influence radiosensitivity, and how this combine with the increased LET radiation are also included in the research program.

One of the topics with really great interest in the radiotherapy community is dose-rate effects. This arises from studies that using ultra-high dose rates leads to the so-called FLASH-effect, where normal tissue sparing effect is observed, while the tumor response appear to not be affected. There is however a broad range of factors within this effect which is not well understood, such as the impact of increasing high dose rate.

The normal tissue sparing effect is also the focus in the research area of spatial fractionation, where delivering a heterogenous dose have demonstrated both normal tissue sparing while favoring tumor control.

A large part of the current studies is focused on in vitro studies, but with the intention to continue and expand into verification studies in in vivo models.

Likely scientific impact and timeliness of the project:

The presented radiobiology program is of very high quality, with a range of important research questions, as well as a high level in the methodology to answer these. Furthermore, the different subprojects within the suggested radiobiology program are very timely.

The biological characterization of high LET radiobiology; what does high LET actually do in a cell, is an important topic right now, as the use of a fixed RBE of 1.1 for proton therapy is heavily discussed. One rational behind using a fixed RBE is that the impacts of the different factors influencing the RBE are not well understood. More knowledge on the cellular responses to increased LET, in vitro models and in in vivo models, will very likely have a great scientific impact, and furthermore have a clinical relevance.

Recommendations for the radiobiology program:

1. Ensure possibilities for in vivo research. This includes nearby animal facilities and possibility for small animal imaging thought into the facility.
2. Ensure access to experimental reference beams (eg conventional proton beams and photon beams)

2. Review of LhARA collaboration's R&D proposal for the Preliminary Activity Phase – Report Accelerator and Technology Session

G. Arduini, P. Bolton, Ch. Carli, M. Haj Tahar

2.1 Scope

The Laser-hybrid Accelerator for Radiobiological Applications (LhARA) formed the basis of the STFC proposal to the UKRI Infrastructure Advisory Committee to establish the Ion Therapy Research Facility (ITRF). The latter included a request for resources for a two-year "Preliminary Activity" to deliver a Conceptual Design Report for the facility and it identified a subsequent, three-year, "Preconstruction Phase" with resources to be sought during the "Preliminary Activity Phase". The first two years of the LhARA proposal coincide with the "Preliminary Activity" (PA) defined in the ITRF proposal, while years three to five are designed to coincide with the Preconstruction Phase.

The LhARA review has taken place on 26-27 October 2022. It featured two sessions addressing respectively:

1. Radiation biology programme (26/10/2022)
2. Accelerator and Technology programme (27/10/2022)

In the following we comment mainly on aspects related to the Accelerator and Technology session.

2.2 Charge

The reviewers were asked to assess and comment on:

- The quality of the science and technology involved in the proposal, the stated scientific and technical objectives, and to consider whether the proposal is likely to achieve those objectives.
- The likely scientific impact of the project within the UK and internationally, and the degree to which the LhARA collaboration's aims and objectives are supported by the relevant scientific communities.
- The timeliness of the project and its relevance with respect to alternative approaches.
- The standing of the groups and collaborators involved in the project, including the track records of the proponents.
- The project management structure, including the alignment between the LhARA collaboration and the ITRF, and the procedures required to ensure that the stated project goals are achieved.
- The scientific, technical, schedule, and financial risks attendant on the project and the degree to which the proposed activity addresses these risks.
- The costing and the proposed milestones against which the project will be monitored.
- The industrial-engagement, outreach, involvement, and engagement plans.

2.3 Programme of the Review

The Accelerator and Technology session included the following presentations:

Project Management

- Overview – C. Whyte (Strathclyde)

Laser-driven proton and ion source (WP2)

- Overview and management – Elisabetta Boella (Lancaster/CI)
- Risk management – Nicholas Dover (Imperial/JAI)
- Diagnostics, instrumentation and targetry – Ross Gray (Strathclyde/CI)

Proton and ion capture (WP3)

- Gabor lens - Christopher Baker (Swansea):

Transfer lines and post accelerator (WP6)

- Stage 1 and Stage 2 vision: Jaroslaw Pasternak (Imperial/JAI/ISIS)
- General facility infrastructure and integration (WP6): Neil Bliss (STFC TD Daresbury)

2.4 Introduction & General Findings

The reviewers thank the speakers, the participants to the Review and in general the LhARA Collaboration for the high quality and clear presentations and for the open discussions that covered the scientific, organizational and resource aspects of the R&D Proposal.

The LhARA facility has been designed to serve two end stations for *in-vitro* radiobiology and one end station for *in-vivo* studies. The main components of Stage 1 of the LhARA accelerator and transfer line complex are:

- laser-driven proton and ion source;
- matching and energy-selection section;
- beam delivery to the low-energy *in-vitro* end station;
- low-energy abort line.

Stage 2 includes the Stage 1 components and in addition:

- injection line for the fixed-field alternating-gradient accelerator (FFA)
- FFA;
- the extraction line
- the high-energy abort line;
- beam delivery to the high-energy *in-vitro* end station;
- transfer line to the *in-vivo* end station.

Proton beams with an intensity of ~10^9 p/pulse with energies between 10 and 15 MeV will be delivered in pulses few ns long to the low-energy *in-vitro* end station at 10 Hz providing average dose rates exceeding 70 Gy/s and instantaneous dose rates exceeding 10^9 Gy/s. The high-energy *in-vitro* and the *in-vivo* end stations will be served by ~10^9 p/pulse with energy between 15 and 127 MeV and by ~10^8 C^{6+} ions/pulse with energies up to 33.4 MeV/u delivered in pulses of a few tens of ns providing average dose rates up to 156 Gy/s and 730 Gy/s for protons and carbon ions respectively and instantaneous dose rates exceeding 10^8 Gy/s. The above doses have been estimated for an RMS beam size of 0.25 mm. Spot sizes of 0.25 mm RMS appear to be reachable for the proton ion beams. No estimates have been provided for the Carbon ion beam size.

It is proposed to construct a new purpose-built, energy efficient building. The full building envelope will be erected as part of stage 1 while Stage 2 radiation shielding, equipment, and technical services will be added later.

We appreciate the efforts made by the LhARA collaboration in the refinement of the proposal and in its alignment with the ITRF one, since the last “Pre-publication review of the LhARA pre-CDR” (held on 31/3/2020). The milestones and scope of the Preliminary Phase have been revised to match the available resources. We note that several of the recommendations and observations made in occasion of the previous review have been considered and incorporated in the proposal.

A document collecting the baseline hardware and performance parameters of the various components of the accelerator has been created. This will serve as a means to guarantee coherence in the design of the key elements of the facility and will provide a useful reference for the users.

A detailed schematic of the current baseline configuration is already available and used to identify all the required devices for input to the CAD design and cost model. It adopts a Device Naming Convention with the intention that the Device Names will be implemented in the control system.

2.5 Quality of the science and technology involved in the proposal, the stated scientific and technical objectives, and to consider whether the proposal is likely to achieve those objectives

Findings

The proposal is combining the use of a laser driven ion source powered by a commercially provided high repetition rate (10 Hz) 100 TW/25 fs laser impinging on a thin target, a series of high gradient Gabor lenses for focusing and energy/ion charge state selection and a scaling Fixed Field Accelerator (FFA) with variable extraction energy.

Based on the available experience in the collaboration and in other laboratories there is confidence that the goal of achieving pulses of 10^9 protons at 15 MeV with an energy spread of +/-1-2% is reachable, the main challenges remain the operation of the source at high repetition rates (10 Hz) reliably and reproducibly with major concerns related to the target integrity and the impact of debris on the operation at high repetition rate. The definition of the specifications for carbon ion operation (10^8 C^{6+} ions/pulse at 4 MeV/u) requires significant R&D.

The choice of Gabor lenses operated in DC mode as compared to more conventional solutions (e.g., normal conducting solenoids) has been driven by the aim of minimizing power consumption and avoiding bulky magnets and power converters. Similar devices (but operated at significantly lower plasma density and for a different purpose) are used in particle physics experiments (e.g., ALPHA at CERN).

A scaling variable-energy FFA post-accelerator is proposed for its compactness and the expected capability of maintaining the longitudinal and transverse properties of the bright beam delivered by the laser-ion injector.

Comments

The LhARA proposal presents an outstanding example of novel science and technology with major impact on the quality of life via a reasonably doable yet challenging plan. It aims to ultimately usher new science and supporting technology that advances and even transforms ion beam radiotherapy as cancer treatment with high therapeutic index. Adequate levels of relevant biology, physics, chemistry and engineering must be sustained for a long interval to eventually realize clinical application and ultimately improved patient experience that will include important post-treatment issues.

The state of the art for accelerator technology is commensurately advanced. A hybrid accelerator scheme that exploits distinctive features of laser-driven ion sources combined with an FFA post-accelerator is proposed that will be become a core component of a new Ion Therapy Research Facility (ITRF). As a source, reduced laser system requirements render the laser-driven ion source subsystem significantly more feasible. The proposal of conducting initial tests at 1 Hz at SCAPA is the appropriate repetition-rated start. A successful LhARA programme will accomplish what has been sought in the intense laser-plasma community for almost two decades.

Proposed variation and control of ion dose features include ion type, spatial dose profile (transverse and longitudinal), incident ion energy, dose level, dose rates (Ultra High Dose Rates – UHDR - instantaneous and average) and irradiation mode (actively scanned and passive). Proposed Stage 1 and Stage 2 studies of RBE and its dependences will be definitive. This will include exploration of the radiosensitivity with variable oxygen content (hypoxic survival); notably in FLASH and UHDR cases.

The main objectives set for the two-year PA have been revised considering the available funding and resources. The LhARA collaboration has the scientific standing and reputation to raise additional funding, leveraging on the resources allocated.

The proposed objectives remain challenging given the limited resources though they appear to be achievable. The main deliverable of the preliminary phase, i.e., the completion of a Conceptual Design Report is within reach.

2.6 Likely scientific impact of the project within the UK and internationally, and the degree to which the LhARA collaboration's aims and objectives are supported by the relevant scientific communities

Findings

From the presentations on 26/10 it appears that there is a general consensus among the medical and radiobiology international community on the need of systematic *in vitro* and *in vivo* research to establish the dependence of radiobiological effectiveness (e.g. cell survival rate) of proton and ion radiation in normal and tumour cells/tissues on several irradiation parameters (e.g. spatial and temporal dose distribution, beam type and energy, …) and irradiation conditions (oxygen levels, drugs,..). This is required to elucidate the mechanisms leading to the observed benefits of FLASH therapy or Spatially Fractionated Radiation Therapy (SFRT) in terms of reduction of the toxicity on normal tissues and enhanced tumour control and to define the paradigm for future hadron therapy.

The above need demands for flexible sources of proton and ion beams capable of delivering ultra-high instantaneous dose rates (up to $10^8 – 10^9$ Gy/s) and high average dose rates (10-1000 Gy/s) with small (sub-millimetric) spot sizes, though no detailed user requirements have been formulated during the review.

The study of ion beams (Carbon Ions and possibly other heavier ion species like Neon and Argon) is mandatory given the larger effectiveness in killing cancer cells.

An accuracy in the measurement of the dose delivered on a pulse-by-pulse basis at the level of 10% or better is required.

To our knowledge no dedicated facility for radiobiological studies that can deliver beams with the above-mentioned characteristics exists or is part of a current project. Existing conventional hadron therapy centres cannot match the above specifications and/or can dedicate only a small fraction of their operation time to systematic radiobiological studies.

Comments

The proposed concept of Laser Hybrid Accelerator meets the requirement for ultra-high dose rates and temporal and spatial structure necessary for conducting the experimental programme proposed by the medical and Radiobiology community and above outlined. These studies will open the way to new optimal clinical treatment protocols (e.g. FLASH therapy or SFRT) shaping the developing field of hadron-therapy in the UK and worldwide.

The LhARA programme will represent the first definitive application of laser-driven energetic ion sources to ion beam radiotherapy (IBRT). As such, it will be a long-awaited result of immediate global impact both in terms of basic supporting science and novel clinical development. For almost two decades this has been an important (and enthusiastic) global quest for accelerator advancement and medical application. Proposed developments can redefine radiotherapy; opening new doors for

continued cancer research that improves treatment, post-treatment and quality of life in general for patients. In summary, this novel UK platform promises to attract major users and collaborators and to open several other uses of accelerators.

Recommendations

Continue and strengthen the collaboration between the medical and radiobiology and the accelerator communities. This is vital in the refinement/revision of the parameters with the evolution of the project as R&D progresses and options are investigated.

2.7 Timeliness of the project and its relevance with respect to alternative approaches

Findings

The project is expected to answer the compelling demand by the radiobiology and medical communities for flexible sources of proton and ion beams capable of delivering ultra-high instantaneous dose rates and high average dose rates with small (sub-millimetric) RMS beam sizes to understand the mechanisms by which the biological response to ionising radiation is determined by the physical characteristics of the beam and tumour environment. No dedicated facility exists that can deliver beams with the required characteristics.

Comments

UK has an advanced expertise and infrastructure to develop laser technologies and targets to produce intense pulses of proton and/or ion beams. UK institutes are also at the forefront in the design and construction of plasma lenses and compact FFAs. The latter gained maturity over the last 20 years thanks to the development in Japan, the UK and the US of the scaling and non-scaling FFA concepts and thanks to on-going international collaborations. STFC has demonstrated its leadership in this field. All these technologies are key ingredients for the Laser Hybrid Accelerator. 100 TW laser systems operating at 10 Hz are now available commercially.

With the advent of very short ion bunch durations (and therefore ultra-high instantaneous rates), new radiobiological science becomes relevant and must be well understood. The anticipated accessibility, flexibility and high throughput of the UK platform is essential and strong global interest is anticipated. Serving also to highlight progress with alternative approaches, there are many direct and indirect positive aspects of this work.

The proposal and its associated R&D programme are therefore timely and promise to deliver beams whose characteristics are presently not achievable with conventional ion sources.

2.8 Standing of the groups and collaborators involved in the project, including the track records of the proponents

Findings

The development of the laser-driven source will see the involvement of Cockcroft and John Adams Institutes' scientists at Imperial College, Lancaster and Strathclyde Universities and by scientists at Queen's University, Belfast. It will benefit of the world-class technical infrastructure at the Scottish Centre for the Application of Plasma-based Accelerators (SCAPA).

The capture and energy selection system, including the Gabor Lenses, will be designed by scientists at Swansea University and Cockcroft Institute's scientists at Manchester University. They have already

successfully contributed to the design of a Gabor Lens in a Penning trap for the ALPHA experiment at the CERN Antiproton Decelerator.

The design of the beam lines and of the FFA will be conducted by John Adam's Institute Scientists at Imperial College and Royal Holloway, while engineering support and specifications of the technical services for the facility will be provided by the Technology Department at STFC Daresbury. These have contributed to the design and construction of the first non-scaling fixed-field alternating-gradient (FFA) particle accelerator at Daresbury Laboratory.

The STFC Technology Department oversees the overall design of the facility infrastructure and technical services providing its experience, multidiscipline technical expertise, approved radiation site authorisation and electrical power capability. The same team has recently built the Advanced Oncotherapy Validation & Verification Site infrastructure at Daresbury, which has similar requirements to those of this project.

Many key researchers of this proposal are globally well-engaged and well-informed about their specific fields. Some other collaborative members are named here to emphasize this strong point in favour of the effort. This includes: the Institute of Systems, Molecular and Integrative Biology, the Medical Research Council - Oxford Institute for Radiation Oncology, AstraZeneca, NHS (Clatterbridge Cancer Centre, The Christie, University Hospitals Birmingham, Imperial College Healthcare), the University of Glasgow, Imperial College London (The Institute of Cancer Research), University of Birmingham, University of Liverpool, Hampton University, the Leo Cancer Centre, Maxeler Technologies, the Rosalind Franklin Institute, the National Physical Laboratory, the Netherlands Cancer Institute, Institut Curie, INFN Catania, CERN and Corerain.

Comments

The LhARA Collaboration is composed by world class scientists and engineers and groups with a long-standing experience in the design and construction of the key components of the accelerator and the facility. They have access to unique facilities in the UK (e.g., SCAPA) and are involved in several international projects for particle physics experiments (e.g., ALPHA) and for the development of new acceleration techniques (e.g., AWAKE, MICE)

There is little doubt that additional partnerships will likely emerge as the proposed work progresses and continued funding is sought. Diverse and expansive support brings access to multiple sites for supportive research and experienced skill where it will be needed to help guarantee success. This large collaboration helps to assure researchers and results of global stature.

2.9 Project management structure, including the alignment between the LhARA collaboration and the ITRF, and the procedures required to ensure that the stated project goals are achieved

Findings

The reviewers have been presented with the ITRF and LhARA Organizational Breakdown Structures. The ITRF project will be carried out through four Work Packages (WP):

0. Management and CDR.
1. LhARA;
2. ITRF Facilities and Costing; and
3. Conventional Technology.

The LhARA collaboration is responsible to deliver the Conceptual Design Report for a Radiobiology irradiation Facility based on the Laser Hybrid Accelerator concept (ITRF WP1) and to conduct the preliminary R&D for the development of a high repetition rate laser ion source, Gabor lenses and ion-acoustic dose deposition profile measurement, and to design a post-accelerator, beam transfer lines and irradiation end stations. The evaluation of the conventional technical facilities, with the aim of providing a cost estimate of the facility, is supported by the Technology Department at STFC Daresbury Laboratory.

The LhARA Project includes six work packages (WP):

- WP1- Project Management;
- WP2 – Laser Driven proton and ion source;
- WP3 – Proton and ion capture;
- WP4 – Ion acoustic dose-deposition profiling;
- WP5 – Novel, automated end-station development;
- WP6 – Facility design & integration.

During the Accelerator and Technology session the activities related to WP1,2,3 and 6 have been presented.

The LhARA Project Management Board includes a Principal Investigator, a Project Scientist, a Project Manager and a Project Management Office. The LhARA Project Management Board reports to both the LhARA Collaboration Executive Board and the ITRF Project Team. During the PA, 19 milestones (M1 to M19) are identified for quarterly reporting to the ITRF project as deliverables (correspondingly D1 to D19).

Comments

Significant effort has been dedicated in the alignment of the LhARA and ITRF proposals and in the integration of the two project structures. The Organization Breakdown Structures of ITRF and LhARA and their interfaces are well defined. A detailed set of milestones and their timeline are spelled-out for the various Work Packages as part of the scope of work to be carried out by the LhARA Collaboration under the ITRF PA. Reporting lines are defined and attention is given to progress reporting to ITRF Management and its preparation.

Due attention is given to Quality Assurance and Sustainability: Device Naming Conventions have been adopted from the very beginning with the intention of implementing the Device Names in the control system and a Concrete Sustainability Appraisal will be produced.

2.10 Scientific, technical, schedule, and financial risks attendant on the project and the degree to which the proposed activity addresses these risks

Findings

A detailed list of technical, schedule and financial risks has been presented for LhARA WP1, 2, 3 and 6 together with the mitigation measures. The funding of the ITRF WP1 does not cover the full programme outlined in the initial R&D proposal for the preliminary phase of LhARA and the milestones and objectives of this phase have been updated considering the available resources.

The Laser Target represents one of the major challenges for the project in order to guarantee the necessary reliability and reproducibility of the beam parameters and the project team has recognized the criticality of the associated R&D that should follow immediately the exploration of the parameter

space of the beam characteristics (energy, flux, divergence for different ion species) provided by the source at low repetition rate with the established targetry and beam diagnostics.

The objectives of the R&D preliminary phase for the development of the Gabor lens have been significantly reduced and the Gabor test bench ordering and assembly is no more part of the funded programme.

The design of the optics of capture and energy selection system and of the Stage 1 beam lines is advanced both with solenoids (with the exception of the Wien filter) and Gabor lenses. The design of the optics of the Stage 2 beam line is also well advanced.

The motivations have been presented for the choice of a scaling variable-energy FFA post-accelerator as compared to a Rapid Cycling Synchrotron.

Comments

Notable scientific and technical risks include targetry associated with the laser-driven ion source and the Gabor lens associated with ion capture, energy selection and beam matching as well as in the design of the variable energy scaling FFA.

In the proposed schedule, these risks are confronted early in Stage 1. Major project risks are listed in an evaluated risk register with identified mitigation measures. The timing of Stage 1 relative to Stage 2 is appropriate for assessing many risk mitigations. Also, initiating building construction during Stage 1 is helpful.

Benchmarking of simulation results with experimental studies using state-of-the-art diagnostics and targetry at the SCAPA facility are essential. The intended dedicated laser diagnostic platform for feedback and control also addresses early source and beam tuning issues. The identified risk of insufficient resources and beam time for ion source development is addressed by established ongoing collaboration with other groups for expertise, possible beam time with other lasers and computer time at other places. A higher power commercially available laser system can be purchased if the risk of inadequate bunch parameters becomes significant (i.e., in terms of bunch charge, flux and kinetic energy). The targetry risk is addressed in part with an active programme to explore the performance of a large variety of target types (such tapes, gases and liquids). Dedicated bench testing experiments will highlight risks associated with repetition-rate and long-term machine operation (including debris issues from the target, shot-to-shot bunch stability and activation in the target area).

The reduction of the R&D programme for the Gabor lens resulting from the adaptation of the program to presently available resources, will entail a delay in the demonstration of the feasibility of the required plasma density. The risk associated with Gabor lens development is mitigated in part by selection of high field solenoids (HFS) as an alternative. Simulations and experimental tests outline a cautious progressive step-by-step plan to scale up the Gabor lens toward desired levels (i.e., in terms of the magnetic field, electric voltage, plasma density and focal length). The large divergence of the beam leaving the target implies stringent requirements for the linearity of the focusing and, in turn, homogeneity of the electron plasma. The Gabor lenses will serve as well to select, together with the magnetic elements further downstream, the ion species. A few particles of unwanted beam leaving the source with small angles may still not be removed and pollute the beam.

Given that the maximum repetition rate (10 Hz) will be determined by the laser ion source, also Rapid Cycling Synchrotrons (RCS) appear to be well suited for the post acceleration with variable energy operation. RCS will be of comparable size to the FFA, it will require a simpler magnet design (possibly

with lower power consumption but a likely more costly power converter) and an RF system with smaller apertures. Moreover, the FFA solution implies that the extraction energy fixes the injection energy (fixed ratio between beam rigidities at injection and extraction). An assessment of the FFA tolerance to imperfections is deemed essential to demonstrate the capability to vary the beam energy and to extract the beam at the same location in a reproducible way. FFA tunability is a major question that should be addressed. The accelerator team has devised several ways how to tune the machine (by implementing trim coils to correct for possible sources of imperfections for instance). However, a more detailed analysis, including operational considerations should be performed. Despite the aforementioned points, it is noteworthy to mention that the lessons learned from the RACCAM project and the expertise of the accelerator physicists in charge are highly valuable and give more confidence about the feasibility of the variable energy FFA.

It is not obvious which option is more tolerant to space charge effects. It should be noted that no scaling variable energy FFA has been built so-far and the injection line will have to be retuned according to the extraction energies and the ion species. In addition, the required beam diagnostics may need careful assessment to facilitate the tunability of the machine. If demonstrated, this will represent a major step forward in the FFA technology. On the other hand, Rapid Cycling Synchrotrons are now widely used and their technology is mature.

First experimental studies conducted by the end of 2024 should continue throughout the entire project at some 'keep-alive' level to assure optimization (and diversity) of targetry and plasma ionic beam optics (in this case the Gabor lens). The application of Machine Learning (ML) and Artificial Intelligence (AI) can serve to further map out and deal with the systematic parameter space of a laser-driven ion source for optimization and control.

In general, the impressive engineering and technology scope of work includes basic components such as vacuum, mechanical/alignment/integration, electrical engineering, control system, cooling systems/HVAC & General services and safety systems. That these details are meant to occur at a scientifically and technically mature site such as STFC is a clear step for risk mitigation.

The continued funding risk is addressed in the current search for funding beyond the present 2-year PA phase. The additional financial risks are associated to the costing methodology and present international situation and are discussed in the following section (Section 11).

Recommendations

Assess in depth possible challenges and limitations of the Gabor lens in addition to the required electron density and plasma transverse size as the required focusing linearity and, in turn, electron density homogeneity and possible beam pollution by other species.

Continue the preliminary preparations to facilitate the implementation of a proton and ion capture system based on more conventional technology (normal conducting or superconducting solenoids and Wien filter) as a possible alternative to the Gabor lens system, if it becomes necessary. As part of the Conceptual Design Report it might be useful to define the timeline for decision on the choice of the design of the capture system consistent with the construction and operation deadlines.

Consider a preliminary design of a Rapid Cycling Synchrotron as a possible alternative to the FFA as post accelerator and compare costs, performance but also tunability and operability of the two options.

A thorough study of direct space charge effects and their impact on beam loss and emittance increase should be carried out. The consequence of direct space charge effects on beam parameters after acceleration should be evaluated and used to estimate possible beam sizes at the end stations.

2.11 Costing and the proposed milestones against which the project will be monitored

Findings

Quarterly deliverables (D1 to D19) are reported (beginning in December 2022 and ending in September 2024) to mark critical achievements.

The ITRF project is supported with £2M over two years. A total of £1.81M are allocated to support the development of LhARA to serve the ITRF:

- £1.49M to support LhARA technical-risk mitigation and preparation of the CDR as part of ITRF WP1
- £0.32M to support the evaluation of the conventional technical facilities and to produce a cost estimate of the facility for inclusion in the CDR as part of ITRF WP2.

The STFC Particle Physics Department has provided £28k in addition to support the optimization of the Stage 1 and 2 beam lines.

The ITRF Project has started on 1st October 2022.

During the PA phase, the total expected (staff and non-staff) cost tallies to about £1.87 M and we assume that the team will be able to secure the incremental portion of £60 k. The contribution of senior scientists has been limited to contain the overall cost of the manpower.

The following guidelines have been used for the cost estimate:

- The capital and staff costs have been estimated in calendar year 2022 based on input from each institution.
- Inflation has not been included.
- VAT (at the rate of 20%) is included in all equipment costs by work package;
- The costs contain no working margin or contingency.

Comments

Many staff scientists are expected to spend only a small fraction of their working time on LhARA. This may induce a risk that some tasks take longer than expected. The scope and cost of the project has been adapted considering the available funding but at present the funding cannot cover both the staff and non-staff costs.

In the present international and economic situation, the high inflation rate introduces some financial uncertainty for the project. It is difficult to envisage further reduction of the resources, given the already limited staff contingent, or an additional reduction of the scope, that would endanger the minimum required R&D defined to provide input for the Conceptual Design Report.

Recommendations

It is recommended to seek compensation for the effect of the inflation considering the exceptional international situation.

Contingency should be addressed at some level.

The proposal has a high potential to validate and introduce innovative and disruptive concepts in the design of accelerators for medical applications. This requires a significant amount of Research and Development. The members of the Collaboration are aware of the need of raising additional funding through various channels (in the UK and outside), including the radiobiology and medical community. This commendable effort should be supported by all means.

2.12 Industrial-engagement, outreach, involvement, and engagement plans

Findings

Industrial partners (SigmaPhi) are interested in the development of the magnets for the FFA solution.

The organisation of peer-group and stakeholder consultation activities, through which the specification of the facility will be defined, are principally the responsibility of Work Package 5 and have not been presented in detail but the Project Management is fully aware of the importance of such activities for the development of the LhARA programme. WP1 is also supporting the organization of outreach and Patient and Public Involvement activities.

Comments

Industrial engagement will be a critical yet natural feature of this effort. This can be especially true for some of the higher risk technologies. In addition to FFA magnet development by SigmaPhi, the RF cavity development and the FFA beam diagnostics can involve working with KURNS, CERN, RAL-ISIS, as well as Kyushu University and J-PARC in Japan. For laser beam time in early stages, it will be important to have alternate laser sites as an alternative or addition to the laser system at SCAPA. Targetry performance has the potential to be a limiter (for repetition-rate in particular) for the laser-driven ion source. In this key technical area global engagement with other laboratories and groups of similar interest must occur. This is also the case for the Gabor lens and ion acoustic components for which global corroboration will be much needed. Collaborations might be established also for the design of alternative solutions like conventional focussing elements and RCS.

The medical community has had a kind of ‘wait and see’ attitude as far as clinical practice is concerned using laser-driven energetic particles. By directly addressing this, physical realization of Stages 1 and 2 can usher a new wave of optimism and activity by the accelerator and medical communities. The definition of medical and radiobiology user requirements/expectations and their translation into specification of the beam parameters and of the beam diagnostic capabilities (including tolerances, precision, accuracy, etc.) are a critical step for the success of the project. This effort is particularly needed for the design of the novel end-station and of the instrumentation required for accurate dose mapping.

Recommendations

The global accelerator community shares broad interest in many of the component technologies. Some outreaching engagements (such as those related to targetry, the Gabor lens and ion acoustic diagnostics) should be sustained for the entire duration of the programme.

A clear definition by the interested users’ community of minimum and optimum requirements to carry out the radiobiological experiments needed to better understand the phenomena relevant to ion therapy would be an additional asset.

Continue the effort in the definition of the medical and radiobiology user requirements/expectations and irradiation modalities and their translation into specification of the beam parameters and of the

beam diagnostic capabilities (including tolerances, precision, accuracy, etc.) Specification of minimum requirements necessary to start with the foreseen scientific program and parameters for optimum exploitation would be useful.

The document describing the baseline parameters of the facility that the reviewers have been presented with, should be extended and regularly reviewed continuing the joint effort among medical, radiobiology and the accelerator communities sharing the ownership of the facility.