First peer-group consultation meeting

14th December 2022

The LhARA collaboration

N. Kumar, K. Long, R. McLauchlan, T. Price, C. Whyte for the
The LhARA Project Management Board

1 Introduction

The first of the series of peer group consultations to solicit input on the specification and design of the end stations for LhARA [1, 2], the Laser-hybrid Accelerator for Radiobioligical Applications, was held on the 14^{th} December 2022. The consultation meeting was held fully online owing to the national train strikes that took place that day. The programme for the meeting (https://indico.stfc.ac.uk/event/668/) was split into two sessions. The morning session received presentations on:

- The mission of the LhARA collaboration and the status of, and plans for, the LhARA project;
- The development of the LhARA initiative in the context of the Ion Therapy Research Facility; and
- The status of the consideration of the conventional, synchrotron-based, fall-back option.

These contributions were followed by presentations on beam instrumentation and the development of culture dishes with thin entrance windows suitable for use with low-energy proton and ion beams. Building on the morning's introductory session, the afternoon comprised of two forums in which the specifications for the *in-vitro* and the *in-vivo* end stations were discussed. This document summarises the discussions that took place and the conclusions and recommendations that were agreed. 51 people from across Europe and beyond registered for the meeting. The conclusions are numbered "**Cn**" and the recommendations are numbered "**Rn**" in the text as they appear. Appendix A summarise the conclusions and recommendations. The maximum attendance on the ZOOM call during the morning session, was 37.

The baseline design [3] for the LhARA facility serves two end-stations for *in-vitro* radiobiology (Stage 1 and Stage 2) and one end-station for *in-vivo* studies (Stage 2). An end-station requirements document [4] was sent to all registered attendees prior to the meeting. Table 1 (overleaf) presents a summary of the specification for the beam parameters that the LhARA facility will provide.

2 Minutes of consultation meeting

The day began with a welcome from Professor Iain McNeish on behalf of Imperial College and the LhARA collaboration. Prof. McNeish emphasised the pressing need for novel therapies in cancer treatment. The morning continued with some introductory presentations to the Ion Therapy Research Facility (ITRF) and the LhARA initiative by Dr. Hywel Owen and Professor Kenneth Long respectively. The aim of the meeting was explained: to consult with the research community to assist in the definition of the specifications for the end stations that will maximise the potential for research using a fully automated, highly flexible system that harnesses the unique properties of laser-driven proton and ion beams. The two Stages in which the LhARA project will be executed and the unique properties of the beams were presented. The associated requirement for novel instrumentation and the operational considerations were also summarised. Professor Karen Kirkby gave an overview of the conventional accelerator option, based on the NiMMS [5] project, and shared her experience

Table 1: Summary of the LhARA beam parameter specifications [3]. These estimates are based on Monte Carlo simulations [1, 2]. The average dose rate is based on the 10 Hz repetition rate of the laser source that is specified in the LhARA baseline.

	Stage 1		**Stage 2**	
	Proton			**Carbon**
Kinetic energy	**12 MeV**	**15 MeV**	**127 MeV**	**33.4 MeV/u**
Beam diameter	35 mm	35 mm	Spot: 1 mm; Uniform: 10–30 mm	
Bunch length	7 ns	7 ns	41.5 ns	75.2 ns
Dose per pulse	7.1 Gy	12.8 Gy	15.6 Gy	73.0 Gy
Instantaneous dose rate	1.0×10^9 Gy/s	1.8×10^9 Gy/s	3.8×10^8 Gy/s	9.7×10^8 Gy/s
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s

of both the facility at the University of Surrey (which inludes a vertical beamline) and of setting up a proton research programme alongside the NHS clinical centre at the Christie Hospital in Manchester. Dr Narender Kumar presented his review of the current status of particle-beam instrumentation along with his research into the use of a gas-jet beam profiler [6]. The morning concluded with Professor Mark Hill sharing his experience of experiments with low-energy particle beams and the development of thin-based sample dishes. Prof. Hill's presentation triggered a discussion of the LhARA design. It was noted that Stage 2 of LhARA incorporates both a high-energy *in-vitro* end-station served with a vertical beam-line and a high-energy *in-vivo* end-station with a horizontal beam-line. Technology to automate exposures in each of the end stations will be required.

The afternoon began with discussion of the specification for the *in-vivo* end-stations and concluded with a discussion of the *in-vitro* end-station. The consensus was that the LhARA facility would offer benefits over existing facilities and that, going forward, more focus should be placed on:

- The radiobiological opportunities arising from the unique time structure that LhARA offers (**R1**);
- The experimental complications arising from using a low-energy proton beam (**R2**); and
- The workflow and required cell-culturing facilities required to support a multi-user, quasi-continuous irradiation facility (**R3**).

These points will form the basis of future discussions as they will have impact on both the high- and low-energy operations, the end-station apertures, building designs, automation, and beam diagnostics.

The following sections highlight key discussion points and summarise the recommendations that were arrived at in this consultation meeting.

2.1 Beam line orientation

The discussion of the LhARA concept led to the conclusion that baseline should not be revised; i.e., the *in-vitro* beamlines should remain vertical whilst the *in-vivo* beam line should remain horizontal (**C1**). The design of the facility is required to accommodate this and requires that each end station has an appropriate specification. Those present highlighted that samples being irradiated will be in dishes, flasks, and multi-well plates which vary in size and can become difficult to seal. In order to keep LhARA as flexible as possible for a range of users it was therefore preferred to be able to keep samples horizontal at all times. This would avoid the need to

seal the dishes and to reduce the potential for cross contamination or the mixing of drugs, inhibitors, markers, or other biologically-relevant substances which may impact the biological results. This choice has an impact on the orientation of all systems within the end station and will be factored into design work.

2.2 Beam size

The 35 mm diameter beam delivered to the low-energy *in-vitro* end station will be sufficient to irradiate samples in 6 well plates and simultaneously irradiate multiple wells of multi-well plates, easily enabling sample replicas. There was interest in smaller beams for spatially-fractionated studies. It was noted that the high-energy end-stations will offer spatial fractionation of beams with mm sizes and that spot scanning would be required in order to irradiate larger samples with these beams. The capability to produce spatially fractionated beams and spot scanning at each of the the (low- and high-energy) end-stations is presently being studied.

2.3 Dosimetry

An upper limit on the desired accuracy of the measurement of integrated dose was agreed to be 5% (**C2**), so that radiobiological factors will contribute the dominant uncertainty in the measurements. In keeping with this, dose repeatability at the level of 5% (**C2**) across multiple cell dishes was preferred. However, provided dosimetry is available for each dish, this repeatability criterion can be relaxed and the measured dose can be factored into subsequent analysis. The dose-measurement-accuracy requirement highlights the need for the end stations to be compatible with appropriate dosimetry techniques such as that being developed in LhARA "Ion-acoustic dose-profile measurement" work package and those identified during the course of the peer-group consultation and during the execution of the LhARA project.

The impact of scattered irradiation on neighbouring samples will need to be evaluated as the design of the end stations mature (**R4**)).

2.4 Energies and beam spectra

Proton beams only will be delivered during Stage 1. Moreover, energy loss in the beam-exit window implies that it is unlikely that ion beams will be delivered to the low energy *in-vitro* end station. The baseline proton-capture energy is 15.0 ± 0.3 MeV. The baseline configuration maintains the possibility to provide beam energies between 12 MeV and 15 MeV. Lower energy proton beams could be delivered but would require modifications to standard cell-culture vessels. The high energy beam spectrum for Stage 2 also has a 2% energy spread. The range of a 127 MeV proton beam in water is approximately 118 mm. The baseline specification is that the high energy end-stations will be served by a 33.4 MeV/u carbon-ion beam. The delivery of a range of ion species is being investigated.

Considering the application of thermoacoustic dosimetry, a 2% beam energy spread would smooth the Bragg peak by an additional 5 mm in the beam direction. This will impact the bandwidth of the thermoacoustic signals.

A paper describing how to reduce the cyclotron energy spread in order to improve the resolution of proton tomography [7] was highlighted. The baseline LhARA lattice includes RF cavities to allow phase rotation to be used to manipulate the longitudinal (energy/time) phase space. The use of the cavities, together with the phase-rotation that can be carried out in the FFA, will be studied with a view to tuning the energy spread and manipulating (potentially increasing) the instantaneous dose rate. A reduction in beam energy spread may benefit thermoacoustic dosimetry. The reduction in energy spread will help most with low energy beam as the energy spread of high-energy beams will have increased by range straggling.

2.5 Particle species

The primary ions to be studied are protons and carbon. Studies [8] have shown that ^{3}He beams have the potential to deliver clinical benefit at a reduced cost compared to carbon ion beams and the study of ^{3}He beams is therefore of interest. The production of helium ions using a laser-driven source will be challenging and will require development within the LhARA programme.

2.6 Dose Rates

The triggerable nature of the laser-driven source offers the potential for "pump-probe" type experiments. The opportunities presented by such novel time structures will be explored at future meetings.

2.7 End-station design

The end station will be served by robots to allow for rapid sample changes and increased throughput. The end station must therefore be sufficient in size to house the robotics and allow access for sample changes whilst maintaining the environmental properties required in the end station during the experiments. The temperature must be controlled with heating and cooling stages to allow a range of sample temperatures. We will seek to understand the temperature ranges and the stability required in future meetings (**R5**).

It is also important to take into consideration the oxygen concentrations from normoxia to hypoxia (1-0.1%) and the impact transporting samples in and out of the end stations has on these conditions.

Particular attention will need to be paid to the beam-exit window through which the beam enters the low energy end-station due to the short range of the 15 MeV protons to ensure as much range in the samples as possible and to minimise the multiple Coulomb scattering which will impact the beam size and uniformity. The distance between the vacuum system, entrance window, and samples must therefore be minimised.

2.8 Cell dishes

The 15 MeV beam will lose significant energy as it enters a standard cell dish. Ideally, the same cell dishes, with known thickness should be used for irradiations on the low-energy and high-energy *in-vitro* beam lines for consistency and commercially available plates/dishes should be selected as appropriate. The specification of proton beam energy between 12 MeV and 15 MeV was chosen with this requirement in mind. However, exposures at lower energy and using carbon ions will require dishes with thinner entrance surfaces to ensure the Bragg peak is within the cell sample. Such irradiations may require bespoke dishes similar to those presented by Mark Hill where the base is formed of Mylar.

2.9 Sample preparation and analysis

The locations of the cell preparation, culturing, incubation, imaging, and testing facilities is paramount. These facilities should be within a short distance of the end stations and accessible via the robotic handling systems to enable both sample preparation and post-irradiation sample processing. This will impact the layout of the irradiation rooms and the facility so that smooth transport and transfer of the samples can be ensured. Particular emphasis must be placed on the minimisation of the pause between samples and users whilst samples are removed from the irradiation room.

2.10 Access Costs and times

In 2018 the cost of access to proton beams ranged from 500 €/hour to 1200 €/hour. Additional charges are made for setup and preparation. These costs vary depending on complexity of experiment. The grading of costs, dependent on how much equipment/effort is required will need to be considered for LhARA operations.

The End-station requirements document [4] specifies that the *in-vitro* end stations will be capable of extended (16–24 hours) routine operation without operator intervention and that the *in-vivo* end station design will maximise the period of intervention-free operation as far as possible without compromising the welfare of the animals. Dedicated periods of beam time for setup and QA and systems development will also need to be scheduled.

2.11 In-vivo considerations

The issue of the range of animals required for the *in-vivo* programme, i.e. whether it was sufficient to plan for rodents only or whether larger animals would also be needed, was discussed. This issue requires further discussion and engagement with a variety of expert groups such as the peer-group that attends the FLASH Radiotherapy and Particle Therapy (FRPT) conference series. The results of *in-vivo* experiments performed using animals larger than rodents is more translatable to to humans. Such experiments will require imaging to register the position of the animal using bones and other organs. The use of contrast agents, e.g. iodine, barium sulphate, can change the rate at which energy is deposited and therefore the depth to which the radiation will penetrate. Use of "window chambers" during animals irradiation needs to be discussed.

Licensing of the facility for *in-vivo* experiments will need to be addressed. As yet, no proton centre has been licensed for *in-vivo* operation in the UK. Requirements for the animal house, such as soundproofing, diurnal stimuli, etc. will have to be considered carefully.

Questions which require further information:

1. Once irradiated, do the animals stay housed in the facility?
2. What legal requirements need to be met?
   Consider the possibility of exploiting or joining with existing animal studies and engage with RADNet, NCRI, and ARR to gain expert advice and to build a user base.
3. Are there requirements for procedures other than irradiation, such as surgery, to be carried out at the facility?
4. Are there issues arising from the transporting of animals between facilities in different locations?

These issues as well as the range of animals required and the licensing considerations will need to be considered in further discussion of the *in-vivo* end station specification (**R6**).

There was consensus that it will be important to consider carefully whether the LhARA facility should be co-located with an animal house or whether it will be sufficient to partner with an existing facilities (**R7**). If the partnership model is preferred over the co-location model, it will be important to articulate clearly how issues arising from transportation and temporary accommodation at the radiation facility will be addressed. Since there are few sites in the UK that presently have an appropriate animal house, the choice of the co-location model will imply either that an animal house is constructed in parallel or that the choice of location will be limited.

Significant work has been conducted in the USA via voluntary of pet dogs. It is therefore important to note the locations of centres in the UK which currently offer radiation therapy for pets as listed below.

2.11.1 Centres which currently offer radiation therapy to pets in the UK

- Southfields Veterinary Specialists
- University of Liverpool
- Veterinary School, University of Cambridge
- Veterinary School, University of Glasgow
- Veterinary School, University of Edinburgh
- Veterinary School, Animal Health Trust, Newmarket

3 Conclusion

The first user consultation meeting for the LhARA facility was held in December 2022. The outcomes have been detailed in this report including facility decisions such as beam line orientations, discussion points, and areas for future development. The second consultation meeting will be hosted in Birmingham in June 2023 and focus on *in-vitro* studies and the impact of the low energy beam line on end-station design. Future meetings will focus on the legislation and restrictions arising from the need for animal work.

References

[1] G. Aymar, T. Becker, S. Boogert, M. Borghesi, R. Bingham, C. Brenner, P. N. Burrows, O. C. Ettlinger, T. Dascalu, S. Gibson, T. Greenshaw, S. Gruber, D. Gujral, C. Hardiman, J. Hughes, W. G. Jones, K. Kirkby, A. Kurup, J.-B. Lagrange, K. Long, W. Luk, J. Matheson, P. McKenna, R. McLauchlan, Z. Najmudin, H. T. Lau, J. L. Parsons, J. Pasternak, J. Pozimski, K. Prise, M. Puchalska, P. Ratoff, G. Schettino, W. Shields, S. Smith, J. Thomason, S. Towe, P. Weightman, C. Whyte, and R. Xiao, "LhARA: The Laser-hybrid Accelerator for Radiobiological Applications," *Frontiers in Physics* **8** (2020).

[2] The LhARA consortium, "The Laser-hybrid Accelerator for Radiobiological Applications," Tech. Rep. CCAP-TN-01, The Centre for the Clinical Application of Particles, Imperial College London, 2020. `https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Communication/Notes/CCAP-TN-01.pdf`.

[3] The LhARA collaboration, "Baseline for the LhARA design update," Tech. Rep. CCAP-TN-11, The Centre for the Clinical Application of Particles, Imperial College London, 2022. `https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Communication/Notes/CCAP-TN-11-LhARA-Design-Baseline.pdf`.

[4] **LhARA** Collaboration, N. Bliss *et al.*, "LhARA: End-station requirements document," Tech. Rep. LhARA-Gov-PMB-2022-01, 2022. `https://ccap.hep.ph.ic.ac.uk/trac/raw-attachment/wiki/Research/LhARA/Documents/LhARA-Gov-PMB-2022-01.pdf`.

[5] M. Vretenar, V. Bencini, E. Benedetto, P. Foka, M. Khalvati, A. Lombardi, M. Sapinski, and D. Tommasini, "The Next Ion Medical Machine Study at CERN: Towards a Next Generation Cancer Research and Therapy Facility with Ion Beams," in *Proc. IPAC'21*, no. 12 in International Particle Accelerator Conference, pp. 1240–1243. JACoW Publishing, Geneva, Switzerland, 08, 2021. https://doi.org/10.18429/JACoW-IPAC2021-MOPAB413.

[6] N. Kumar, A. Salehilashkajani, H. Zhang, M. Ady, P. Forck, J. Glutting, O. Jones, R. Kersevan, T. Marriott-Doddington, S. Mazzoni, A. Rossi, G. Schneider, S. Udrea, R. Veness, and C. Welsch, "Non-invasive beam profile monitor for medical accelerators," *Physica Medica* **73** (2020) 173–178.

[7] A. T. Herrod, A. Winter, S. Psoroulas, T. Price, H. L. Owen, R. B. Appleby, N. Allinson, and M. Esposito, "Optimal Configuration of Proton-Therapy Accelerators for Relative-Stopping-Power Resolution in Proton Computed Tomography," *Phys. Rev. Appl.* **18** (Jul, 2022) 014020.

[8] F. Horst, D. Schardt, H. Iwase, C. Schuy, M. Durante, and U. Weber, "Physical characterization of 3He ion beams for radiotherapy and comparison with 4He," *Physics in Medicine & Biology* **66** (2021).

A Summary of conclusions and recommendations from the first peer-group consultation meeting

The conclusions drawn from the discussions at the first peer-group consultation meeting and the recommendations made are summarised here. This Appendix will be reproduced as a record of the outcomes of the first consultation meeting in the end-station requirements document [4].

Conclusions

C1: The case for a change to the present baseline beam-delivery concept for the low and high energy *in-vitro* end stations and the *in-vivo* end station is not compelling and therefore the present baseline should be retained.

C2: A specification of 5% as the upper limit on the accuracy of the integrated dose measurement and its repeatability is sufficient for the dose-measurement uncertainty not to dominate the error budget of biological experiments.

Recommendations

R1: The radiobiological opportunities arising from the unique time structure that LhARA offers should be investigated.

R2: The experimental complications arising from using a low-energy proton beam must be considered carefully.

R3: The workflow and required cell-culturing facilities required to support a multi-user, quasi-continuous irradiation facility must be carefully planned.

R4: The impact of scattered irradiation on neighbouring samples must be evaluated carefully.

R5: The temperature ranges and the temperature and oxygen level stability required must be carefully considered.

R6: Development of the specification of the *in-vitro* end station and its operation should include careful consideration of the range of animals required, the location of animals pre and post-irradiation, the possibility of collaboration with existing animal-handling facilities, and the requirements for procedures other than irradiation to be carried out at the facility?

R7: Careful consideration should be given to the relative merits of co-locating the LhARA facility with an animal house or partnering with an existing animal house located at a distance from the LhARA facility.