The Laser-hybrid Accelerator for Radiobiological Applications

End-station requirements document

N. Bliss, A. Giacca, K. Long, R. McLauchlan, J. Parsons, T. Price, C. Whyte for the
The LhARA Project Management Board

1 Introduction

The baseline design for the LhARA facility [1–3] serves two end stations for *in-vitro* radiobiology and one end station for *in-vivo* studies. At Stage 1, proton beams with kinetic energy between 12 MeV and 15 MeV will be provided to the "Low-energy *in-vitro* end station". At Stage 2, the "High-energy *in-vitro* end station" and the "*In-vivo end station*" will be served by proton beams with kinetic energy between 15 MeV and 127 MeV and by ion beams, including C^{6+}, with energies up to 33.4 MeV/u. The large instantaneous and average dose rates that will be provided are summarised in table 1.

Table 1: Summary of expected maximum dose per pulse and dose rates that LhARA can deliver [1–3]. These estimates are based on Monte Carlo simulations. The average dose rate is based on the 10 Hz repetition rate of the laser source.

	protons			**carbon**
Kinetic energy	**12 MeV**	**15 MeV**	**127 MeV**	**33.4 MeV/u**
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

The beam parameters that will be provided differ significantly from those which are currently available for the study of radiation biology at clinical or research facilities. The key features of the LhARA beams are:

- Triggerable production of short, intense pulses at a repetition rate of up to 10 Hz;
- The time structure of the beam can be varied to facilitate studies of, for example, reaction kinetics;
- Bunches with a minimum length of 10 ns will be provided to the Low-energy *in-vitro* end station;
- Bunches with a minimum length of 40 ns can be provided to the High-energy *in-vitro* and the *In-vivo* end station; and
- The dose distribution at the Low-energy *in-vitro* end station is quasi uniform over an area of approximately $3.5 \times 3.5\,\mathrm{cm}^2$; and
- The dose distribution at the High-energy *in-vitro* and the *In-vivo* end station can be varied from an intense spot with diameter ~ 1 mm to an almost uniform dose distribution over a circular area with a maximum diameter of between 1 cm and 3 cm.

The provision of a small beam spot at the Low-energy *in-vitro* end station and the manipulation of the beam to produce a more conventional time structure will be studied during the Preliminary Activity.

The unique features of the beams will allow the exploration of radiation biology in regions of parameter space that have not yet been studied. The specification of the end stations for LhARA must maximise the discovery reach of the facility. This will require the incorporation of novel, beyond state-of-the-art instrumentation. The *in-vitro* end stations must be capable of extended (16–24 hours) routine operation without operator intervention. This will require automation, climate and temperature control, and systems by which samples can be conveyed into and extracted from the radiation area without breaking the search. The design of the *In-vivo* end station must maximise the period of intervention-free operation as far as possible without compromising the welfare of the animals.

This document summarises the requirements for LhARA end-stations. The requirements will be developed and refined through discussion with the community of potential users. A series of User Consultation meetings are planned [4], each of which will be summarised in an annex to this document. The document will be re-issued from time to time so that it defines the current specification as the consultation process evolves.

2 LhARA baseline

This section contains a precis of the LhARA baseline which is documented in [1]. As outlined above, LhARA provides beam to three end stations as indicated schematically in figure 1 as areas highlighted in purple. The Low- and High-Energy *in-vitro* end stations located on the floor above the accelerator and are served by vertical beam lines. The *In-vivo* end station is located on the same floor as the accelerator and served by a horizontal beam line.

The baseline was developed following LhARA internal review of options with due consideration of appropriate staging. LhARA is divided into six operational rooms or areas by shielding walls. A beam shutter is provided in front of each wall to stop beam from entering the next room. This allows rooms to be isolated, so allowing independent operation and to facilitate the build. The six rooms are:

Laser Room: The laser will be accommodated in its own room allowing appropriate environmental control independent of the rest of the facility.

Target Room: The laser beam will be brought to a focus on the target. The first two beam line elements, both Gabor lenses, are part of the integrated target/capture system and so are sited within the target room to produce a parallel beam.

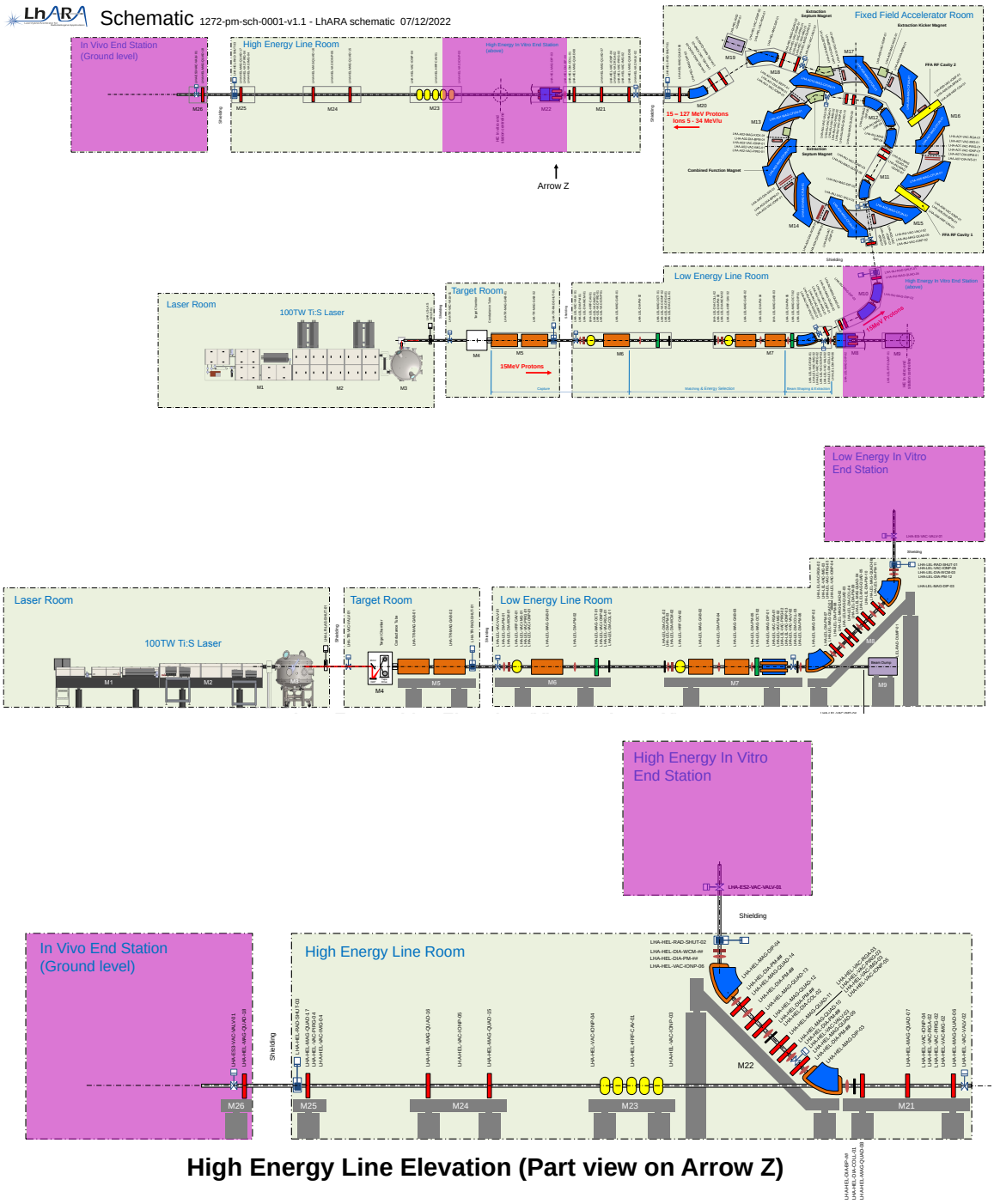
Low Energy Line Room: The elements in this area provide beam collimation, energy selection and beam transport to the Low-energy *in-vitro* end station. In addition, a beam dump, a switching magnet, part of the injection line for the FFA and the vertical arc which directs beam into the Low-energy *in-vitro* end station are sited in this room.

Fixed Field Accelerator Room: This room includes all the post acceleration systems, part of the injection line, the transfer line taking beam to the High-energy *in-vitro* end station and a beam dump.

High Energy Line Room: This room accommodates the beam transport lines serving the High-energy *in-vitro* and *In-vivo* end stations and a beam dump.

End Station Room: This room is on the ground floor to provide the best access for in-vivo irradiations using a horizontal beam line.

The vertical arcs required to supply the vertical beam lines will be integrated on inclined supports. Permanent access for maintenance and repair will be provided. The required equipment for replacement of components will be integrated with the assembly.



High Energy Line Elevation (Part view on Arrow Z)

Figure 1: Schematic diagrams of the baseline layout for LhARA. The top panel shows a plan view of the facility. The central panel shows the side elevation of Stage 1, the Low-energy *in-vitro* end station served by proton beams with energy between 12 MeV and 15 Mev. The bottom panel shows a side elevation of the Stage 2 beam lines serving the High-energy *in-vitro* end station and the *In-vivo* end station with proton beams with energy between 15 MeV and 127 MeV and with ion beams, including C^{6+}, with energies up to 33.4 MeV/u.

3 Instrumentation

It is essential that our cutting edge end-stations are served with well characterised beams, in real time, using instrumentation that will feedback to the accelerator as well as calculate the doses delivered both *in vivo* and *in vitro*. The beam structure and intensity of LhARA dictates that R&D is required to achieve these goals compared to conventional accelerators and dose rates. It is imperative that these technologies are integrated with the end-station design to ensure capability and functionality. In addition, novel cell interrogation techniques are required to allow the time evolution of chemical and biological processes with a resolution less than the 0.1 s between laser shots. The requirements on accuracy and precision of such instrumentation will be governed by the user requirements we will capture during these consultation meetings. The instrumentation splits into two applications which ensure the prescribed dose is delivered.

Measuring beam properties in accelerator: Beam properties along the accelerator chain including beam energy, divergence, emmittance, profile, and current are measured using techniques such as Faraday cups, scintillator screens inserted into the beam, beam loss monitors, and beam position monitors. Often, these techniques are intrusive and destructive to the beam. Fluctuations of such properties can occur from a laser source, and therefore must be measured in a none destructive way for a pulse which is delivered to the end-station.

Irradiation beam measurements: Measurements of dose and dose profile as delivered to the sample itself must be made on a pulse-by-pulse basis. The instantaneous dose rates of the LhARA pulses will prove challenging for standard ionisation chambers due to ion recombination. Technologies such as scintillating fibres, secondary electron emission monitors, gas profilers, and ionacoustic imaging will be studied and compared against conventional instrumentation to ensure accurate dosimetry at LhARA.

Novel instrumentation to allow time-resolved study of radiation-induced processes: The measurement of the time-evolution of the radiation-induced chemical and biological processes will require the development and deployment of optical techniques capable of operation at repetition rates of at least 10 Hz. The discussion of possible techniques will form part of the user-consultation process.

It is anticipated that, during the consultation phase, an ultra high dose rate proton and He-ion facility will be developed at the University of Birmingham. We propose to exploit this new facility to allow the instrumentation developed for LhARA to be tested. In addition to the specification of beam line and dosimetry instrumentation, the consultation process will capture user requirements for novel instrumentation, such as real-time imaging during irradiation, which will allow novel radiobiological studies to be completed at LhARA.

4 Operational considerations

To reduce variability in experiments it is to essential to control all the conditions and handling before and during the experiment as well as in post-experimental cellular and biochemical analysis. The parameters that must be controlled include the cell-culture conditions during handling, irradiation, and plating of the cells for survival or biological end-point measurements. Particular attention must be paid to:

Cell culture: Automation is required to reduce manual errors in plating and potentially bacterial or viral contamination, to increase standardisation in cell maintenance and increase reproducibility of results that would eliminate concerns about experimental timing (weekend or late night work). Equipment needed here would be a cell imager/microscope, cell counter/FACs machine, centrifuge, cell plater, media handling, plate handling and incubator. Robotic hardware would be needed to go from cell maintenance to plating cells for experiments and distributing them after irradiation to the incubator for cellular growth or for end-point analysis (Proteomics, RNAseq, etc.).

Environmental regulation, oxic versus hypoxia microenvironments: Currently, cells are grown at atmospheric levels of oxygen (21%), which is far from physiological conditions. In normal tissues the oxygen levels fluctuate from 3–9%. However, in tumours, oxygen levels can go below 0.5%. Therefore, a controlled environment room or chamber sourced with carbon dioxide, nitrogen, (to reduce oxygen) and compressed air, and equipped with robotics would be essential to investigate the effect of different oxygen tensions (hypoxia) on cell killing and biochemical changes during irradiation with different ions. In addition, on-site cell culture chambers should be capable of maintaining the 8–9% oxygen levels which reflect more accurately the appropriate physiological human tissue conditions.

Animals: The ability to irradiate tumour bearing animals is essential in determining the biological impact of different particle ions. Specially designed jigs that can hold at least 12 animals, will be essential. These jigs must allow anaesthesia to be administered and tumours to be imaged before each animal is sequentially led through ion beam radiations. There will be the need for human intervention in placing the animals in the custom jigs, but the rest of the process should be automated. A custom jig for imaging and radiation has already been developed at OIRO, this would have to scaled up to be able to hold 12 animals.

Cell Exposure to Different Types of Ions: Horizontal beam lines require the cell plates be rotated into the vertical plane before exposure. The vertical beam lines supplying the *in-vitro* end stations ensure that cells within multi-well plates do not have to be sealed or manipulated in any way prior to irradiation, which will enhance the processing speed and minimise any potential disruption of the cells. The LhARA setup must be more flexible and should allow for all different formats of multi-well plates (6, 12, 24, 48 and 96 wells) as well as dishes and flasks. A vertical beam line would allow the creation of a "conveyor belt" of samples that could quickly and continuously be moved through the beam, enabling sustained high throughput.

Automated Sample Handling and Analysis: Once the cells have been irradiated, they will be assessed for survival, immunologic or molecular analysis. The basic machinery for many immune-staining assays will involve cell washing and dispensing primary and secondary antibodies, and different times of incubation. Then the stained samples will need to be analysed. Similarly, survival analysis involves a period of incubation post-irradiation ($\sim$7-14 days), prior to washing, fixing and staining of colonies. The high throughputs envisaged from LhARA favour automation of these processes.

Biochemical Analysis: Depending on whether the analysis will be for DNA, RNA or proteins, different lysis buffers and conditions will apply. Automated DNA sequencing and potentially RNA sequencing should be available. Protein analysis for mass spectrometry will require more steps and may not be cost effective for automation.

Microscopy: Live-cell imaging will uniquely enable the cellular response to different particle ions to be visualised in real time. Cells will usually contain fluorescently-labelled proteins that can be tracked post-irradiation, or alternatively cell morphology or division can be analysed without the need for fluorescence detection. Appropriate high-end microscopes need to be designed/specified.

5 Version history

13^{th} December 2022; "Final":
Final version of LhARA End-station requirements document released in preparation for the first user consultation meeting.

References

[1] 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.

[2] 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).

[3] 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.

[4] "End station R&D and vertical beam line development." https://ccap.hep.ph.ic.ac.uk/trac/wiki/Research/LhARA/EndStation, April, 2022. Accessed: 2022-12-01.