Second peer-group consultation meeting

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The LhARA collaboration

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The LhARA Project Management Board

1 Introduction

The second of the series of peer group consultations to gather 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 19th June 2023. The consultation meeting was held at the University of Birmingham with the possibility of joining remotely via zoom for international collaborators. The programme for the meeting (https://indico.stfc.ac.uk/event/780/) was split into two sessions as per the first meeting. The second consultation meeting focused on the Stage 1 *in-vitro* end-station which will be served with a 15 MeV proton beam, with specific focus on Recommendations 1-5 as outlined in the previous report.

The day began with presentations on the development of the LhARA initiative in the context of the Ion Therapy Research Facility and was followed by a recap and conclusions of the first consultation meeting; An introduction to the Mary Lyons Centre was made which will be of great importance for future consultation meetings. An announcement was also made regarding the Institute of Physics: Advancing Radiobiology Technology Meeting (https://iop.eventsair.com/art2023). Due to the interest of all those in attendance, these presentations were often followed by lengthy discussions on the topics. Building on the morning's introductory session, the afternoon began with presentations on the impact of the low energy beam on the end-station design and the potential radiobiology. This document summarises the discussions that took place and the conclusions and recommendations that were agreed upon. 31 people from across the globe registered for the meeting, with 14 attending in person and very committed contingent of 10-11 people online. The conclusions are numbered "**Cn**" and the recommendations are numbered "**Rn**" in the text as they appear. Appendix A summarise the conclusions and recommendations across both consultation meetings. The recommendations are struck through once a conclusion has been made regarding these points.

Table 1 (overleaf) presents a summary of the specification for the beam parameters that the LhARA facility will provide (as presented in the first consultation meeting report).

A key point to highlight early in this report was a recommendation from Manjit Dohsanjh and Bleddyn Jones to read the yellow report for the Feasibility Study for BioLEIR [3] (**R8**).

2 Minutes of consultation meeting

The day began with a short welcome to Birmingham by Dr Price before Dr Owens and Prof. Long introduced the Ion Therapy Research Facility (ITRF) and LhARA programmes. The recap of the first consultation meeting by Dr McLauchlan facilitated lots of discussions based on the recommendations highlighted. As further discussions were planned for the afternoon the rest of this document will highlight the key points and not necessarily represent the minutes in chronological order. Each of the **R1-5** will be presented in addition to any new discussions.

Table 1: Summary of the LhARA beam parameter specifications [4]. 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

Dr Sara Wells gave an excellent talk on the Mary Lyon Centre and their work with rodents. Key points to consider are automated animal monitoring, the choice of animals to best reflect the complex models of humans, what pre-clinical work needs to be conducted, and quarantine regulations and conditions for the animals. Sara will be invited as an expert to the next consultation meeting focusing on the *in-vivo* end-stations and animal houses where we aim to cover **R6-7**.

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

The LhARA beam is planned to be triggerable at a maximum repetition rate of 10 Hz. The bunch length will be 7 ns and each pulse will contain 12.8 Gy. The beam structure was immediatly of interest and facilitated discussions on chemical reactions happening on the nanosecond time scale and such a machine could allow studies of this in materials other than water. Further discussions on the timing highlighted an interest in timescales during/after irradiations from nanoseconds up to 10s of minutes depending on the end-point being studied. Having the capability to deliver the dose much more quickly would unlock the potential of studying these shorter time points. The work on "pulse radiolysis" by Peter Wardman was highlighted where chemists have been working for 60 years with pulsed beams, and this now seems applicable to FLASH radiotherapy. Similar studies would be made possible on shorter irradiation times with LhARA.

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

Dr Price presented an updated simulation study of the end-station published in the pre-CDR which included a 100 μm perspex entrance window, a 500 μm thick beam monitor, a cell dish made of Perspex at a thickness of 1.2 mm (to match those currently used on the MC40 Cyclotron), and a 30 μm cell layer. An incident beam of 15 MeV reached the cell layer with a reduced energy of 7 MeV and a stopping power of 6.2 keV/μm. The significant energy loss shows how important every component along the beamline is. Due to the small distance

between the sample and collimator the beam profile is unaffected. Upon discussion it was the feeling of the room that as long as these numbers are parameterised then these values are acceptable.

There was a significant fluctuation within a batch of cell dishes for the thickness of the base of 0.1 mm. In this configuration it translates to a change of 0.5 keV/μm onto the cell layer. During the discussions it was noted that these changes are smaller than the uncertainties in the radiobiology and the LET is still low. As such, the cell base thickness should be controlled but are not the dominant factors in the uncertainties upon any measurements made.

The cell dish bases were discussed, as well as glass dishes and mylar bases. Whilst glass and mylar bases offer the advantage of being more uniform and thinner respectively than plastics, they are also more expensive and a more bespoke solution. Manjit coined a phrase of **"Simple, Robust, Reproduciable, and Cheap"** which has been adopted as a mantra for the experiments and end-stations **(C3)**. Therefore, for the rest of the consultation, the Stage 1 in-vitro experiments will assume the use of plastic cell dishes **(C4)**.

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

This was discussed at length. Whilst the model of quasi-continuous irradiations is new, shared facilities are not. The workflow must be kept as flexible as possible in order to accomodate as many users as possible and their differing requirements.

There are many excellent radiobiological laboratories in existance and the design and contents can be easily replicated. The radiobiology is the time consuming part of this work and as such, focus should be on the movement of samples from the lab to the end-station and back again rather than the layout of the lab space itself.

One key point to be emphasised, was the requirement of an X-ray source to be included in the facility to allow control samples and low LET comparisons to be made with cultures in both the stage 1 and stage 2 *in-vitro* end-stations **(C5)**.

A none exhaustive list of equipment that should be included in the radiobiological lab is given below. This is the list that will be included in the Case Study form, with the ability for a user to request other equipment on the form.

- Class II biological safety cabinets,
- Humidified CO2 cell culture incubators,
- Hypoxia chambers,
- Fridges,
- Freezers (-20 and -80 degrees),
- Microscopes (light/fluorescent),
- Refrigerated centrifuges (various sizes/speeds),
- Ice machine, and
- Ultrapure water delivery system.

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

Scattered irradiation will need to be considered, but without a final design this is difficult at this stage. Simple mitigations such as not irradiating neighbouring wells in a multi-well plate would suffice in the first instance to ensure no unwanted dose is delivered.

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

The end-point was discussed heavily during the day, with each user having different needs depending on the end-point of interest. It was decided that attendees of this and the first consultation meeting would be sent a case study survey to canvas specific requirements. The outcomes of the survey will allow headline experiments to be derived to show the potential of LhARA and the end-stations designed accordingly.

Strong cases were made that temperature control at 37°C is essential for studying early time-points, as well as both oxygen and carbon dioxide levels being controlled. The timescales involved for these parameters is critical, as cells can become none viable after a short number of minutes. Integration of cell transport into the end-stations, and environmental stabilisation therefore need to be carefully considered in order to allow transport in the order of minutes **(C6)**.

The exact temperature and hypoxic level depends upon the studies and end-points, so the end-station will need to be flexible and accommodate these.

3 Conclusion

The meeting facilitated excellent discussions including topics identified in the first consultation meeting, and also new topics such as animal studies. A survey will be sent out to capture details of flag ship experiments for the LhARA Stage 1 facility to all attendees of the Consultation meetings so far. The link to the survey is https://forms.office.com/e/uszHSkq5Xe

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] S. Ghithan, G. Roy, and S. Schuh, *Feasibility Study for BioLEIR*. CERN Yellow Reports: Monographs. CERN, Geneva, 2017. 183 pages.

[4] 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`.

[5] **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`.

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

The conclusions drawn from the discussions at the first and second peer-group consultation meeting and the recommendations made are summarised here. This Appendix will be reproduced as a record of the outcomes of the consultation meetings in the end-station requirements document [5].

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.

C3: Any setup and end-station must be **"Simple, Robust, Reproducible, and Cheap"**.

C4: For the rest of the consultation process, the Stage 1 in-vitro experiments will assume the use of standard plastic cell dishes.

C5: An X-ray source to be included in the facility to allow control sample and low LET comparisons to be made with cultures in both the stage 1 and stage 2 *in-vitro* end-stations

C6: Integration of cell transport into the end-stations, and environmental stabilisation needs to be in the order of minutes to ensure cell viability.

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.

R8: The Feasibility study for BioLIER should be studied.

R9: The user community should be sent a short form to complete highlighting their end-points requirements as these differ greatly between users.