WP5: Novel end station development

Report from 2nd peer-group consultation meeting – 19 June 2023

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WP5: Objectives

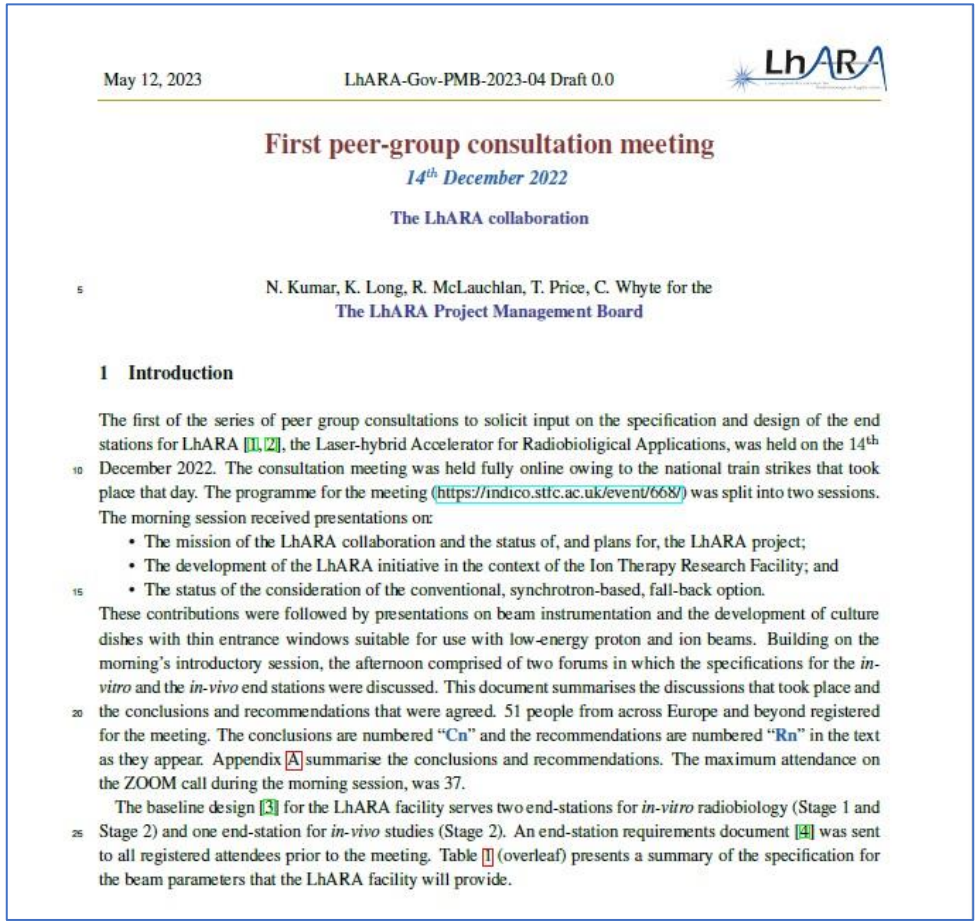
Through peer-group consultation, produce detailed specifications and designs for the in-vitro and in-vivo end stations, the associated dosimetry and the beam diagnostics necessary to characterise the beam delivered to the end stations.

WP5: Tasks and Milestones

- Design LhARA automated cell dish handling and environmental system via user-community consultation
  - De-risk key end station components through experimental measurements at Birmingham
- Assessment of current beam monitoring technology and identification of the R&D required to deliver the diagnostic systems for LhARA
- Development of the design of a test facility at Birmingham capable of delivering kGy/s for use to prove instrumentation and diagnostics developed for LhARA in the Preconstruction Phase

- **M5.1** Initial report on the user requirements for the in-vitro and in-vivo end stations
  - An initial parameter list and end-station specification will be given
- **M5.2** Report on the beam-monitoring technology for LhARA.
  - Will include an options analysis and discussion of cost and R&D requirements
- **M5.3** Report on the user requirements for the in-vitro and in-vivo end stations.
  - Will contain detailed specifications, analysis of layout options, and initial designs for key components

WP5: Report from first peer-group consultation



May 12, 2023 LhARA-Gov-PMB-2023-04 Draft 0.0

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

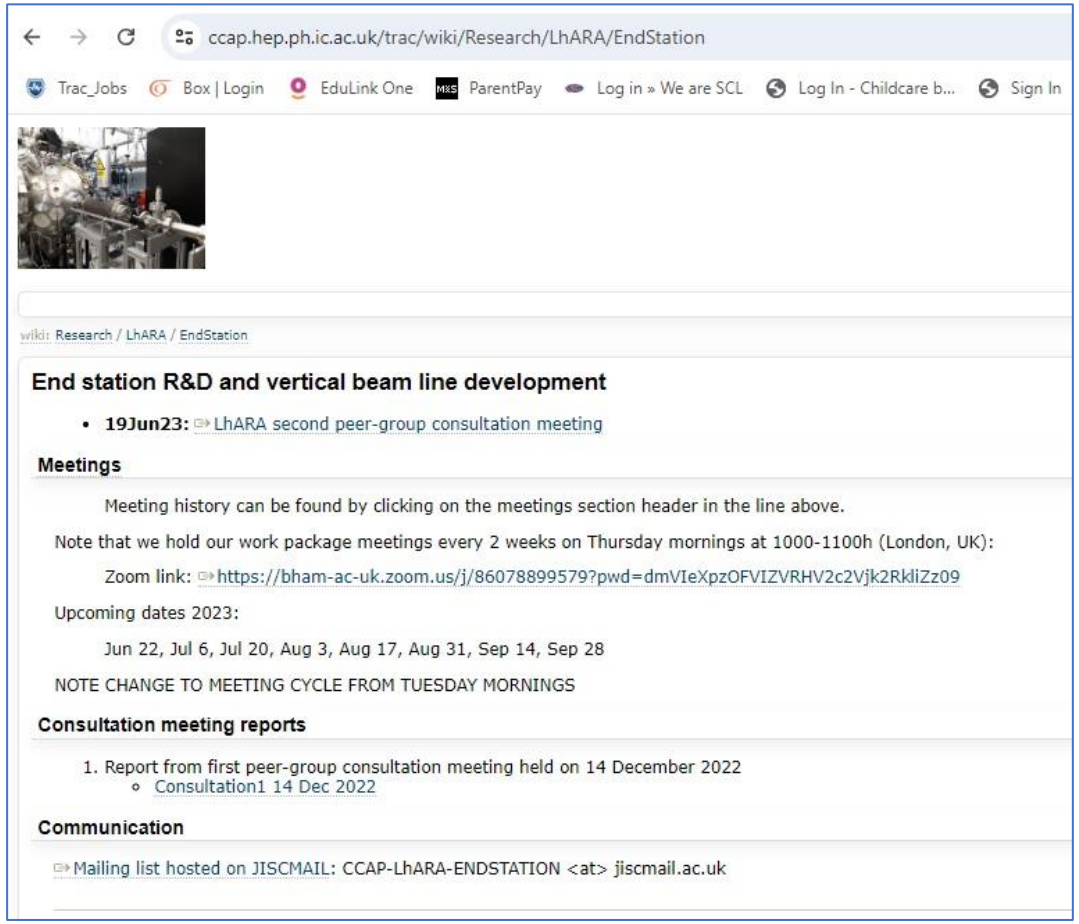
1 Introduction

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 Radiobiological Applications, was held on the 14th 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.



ccap.hep.ph.ic.ac.uk/trac/wiki/Research/LhARA/EndStation

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wiki: Research / LhARA / EndStation

End station R&D and vertical beam line development

- **19Jun23:** LhARA second peer-group consultation meeting

Meetings

Meeting history can be found by clicking on the meetings section header in the line above.

Note that we hold our work package meetings every 2 weeks on Thursday mornings at 1000-1100h (London, UK):

Zoom link: https://bham-ac-uk.zoom.us/j/86078899579?pwd=dmVIeXpzOFVIZVRHV2c2Vjk2RkliZz09

Upcoming dates 2023:

Jun 22, Jul 6, Jul 20, Aug 3, Aug 17, Aug 31, Sep 14, Sep 28

NOTE CHANGE TO MEETING CYCLE FROM TUESDAY MORNINGS

Consultation meeting reports

1. Report from first peer-group consultation meeting held on 14 December 2022
   - Consultation1 14 Dec 2022

Communication

Mailing list hosted on JISCMAIL: CCAP-LhARA-ENDSTATION <at> jiscmail.ac.uk

WP5: Second peer-group consultation

- Birmingham, 19 June 2023: https://indico.stfc.ac.uk/event/780/
  - Focused on the Stage 1 in-vitro end-station which will be served with a 15MeV proton beam, with specific focus on Recommendations 1-5
  - 31 registered; 14 attended in-person; 10-11 attended online
    - Presentations
      - Development of the LhARA initiative in the context of the Ion Therapy Research Facility
      - Recap and conclusions of the first consultation meeting
      - Introduction to the Mary Lyons Centre
    - Breakout discussions
      - Discussed R1-5

WP5: Discussion @ peer-group consultation 2

- **R1: Investigate radiobiological opportunities arising from unique time-structure offered by LhARA**
  - Interest in timescales during/after irradiations from nanoseconds up to 10s of minutes depending on the end-point being studied
  - Peter Wardman "Pulse radiolysis": https://bioone.org/journals/radiation-research/volume-194/issue-6/RADE-19-00016/Radiotherapy-Using-High-Intensity-Pulsed-Radiation-Beams-FLASH--A/10.1667/RADE-19-00016.full
- **R2: Consider experimental complications arising from low-energy proton beam (Stage 1)**
  - Simulation study update
  - Cell dishes – assume use of plastic: "simple, robust, reproducible, cheap"
- **R3: Carefully plan workflow and cell-culturing facilities to support multi-user, quasi-continuous irradiation facility**
  - Whilst the model of quasi-continuous irradiations is new, shared facilities are not.
  - The workflow must be kept as flexible as possible to accommodate as many users as possible and their differing requirements
  - There are many excellent radiobiological laboratories in existence and the design and contents can be easily replicated
  - 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.
- **R4: Evaluate impact of scattered radiation on neighbouring samples**
  - 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: Consider required ranges and stability of temperature and oxygen-levels**
  - Attendees of the two consultation meetings will 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
    - Cells can become none viable after a short number of minutes -> need to allow transport in the order of minutes
  - End-station flexibility important.

WP5: Report from second peer-group consultation

September 19, 2023 LhARA-Gov-PMB-2023-08

Second peer-group consultation meeting

19th June 2023

The LhARA collaboration

N. Kumar, K. Long, R. McLauchlan, T. Price, C. Whyte for the
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.

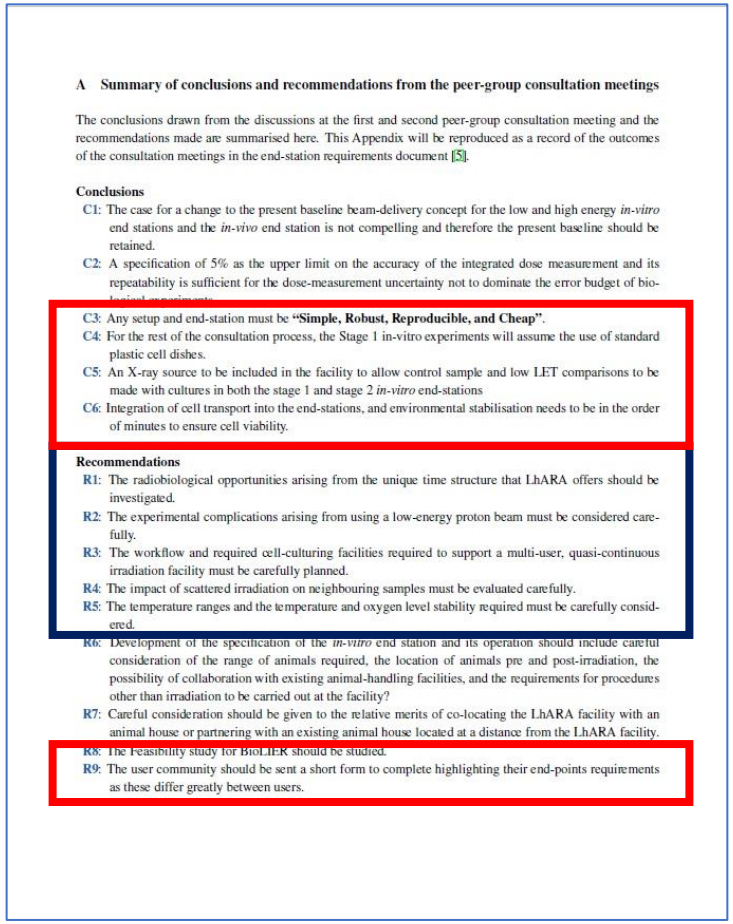
The day began with presentations on the development of the LhARA initiative in the context of the Ion Therapy Research Facility and was followed by a recap and conclusions of the first consultation meeting; An introduction to the Mary Lyons Centre was made which will be of great importance for future 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.



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 BioLEIR 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.

WP5: Report from peer-group consultations 1& 2

Conclusions

1. Baseline to be retained
2. Upper limit on accuracy and repeatability of dosimetry = 5%
3. **Simple, robust, reproducible, cheap**
4. Assume use of standard plastic cell dishes for stage 1 & 2 in-vitro end-stations
5. Integration of cell transport into the end-stations, and environmental stabilisation needs to be in the order of minutes to ensure cell viability.

Recommendations

1. Investigate radiobiological opportunities arising from unique time-structure offered by LhARA
2. Consider experimental complications arising from low-energy proton beam (Stage 1)
3. Carefully plan workflow and cell-culturing facilities to support multi-user, quasi-continuous irradiation facility
4. Evaluate impact of scattered radiation on neighbouring samples
5. Consider required ranges and stability of temperature and oxygen-levels
6. Careful consideration required for in-vivo end-station regarding all aspects of animal-handling (Stage 2)
7. Consideration of location of LhARA relative to animal house
8. The Feasibility study for BioLEIR should be studied
9. Questionnaire to end-users

WP5: Consultation 3, November 2023 (TBC)

- Focus on the in-vivo end-stations and animal houses;
- Aim to cover R6-7:
  - R6: Careful consideration required for in-vivo end-station regarding all aspects of animal-handling (Stage 2)
  - R7: Consideration of location of LhARA relative to animal house