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September 3, 2024

Ion Therapy Research Facility / LhARA

Bridging period 1; project definition

The ITRF/LhARA collaboration

Bridging resources of £2M have been provided through the UKRI Infrastructure Fund to continue the development of the Laser-hybrid Accelerator for Radiobiological Applications (LhARA) to serve the Ion Therapy Research Facility (ITRF) over the period 1$^{\text{st}}$ October 2024 to 30$^{\text{th}}$ September 2026. This document defines the scope of work to be carried out by the ITRF/LhARA collaboration over the 2-year Bridging Period (BP1). The overarching goal is to deliver a proposal for the staged implementation of the facility.

The UKRI Infrastructure Fund provided £2 million over the period October 2022 to September 2024 to support a Preliminary Activity (PA1) to kick-start research on the next generation of radiotherapy treatments for cancer. The objectives of ITRF PA1 were to:

- Prepare a conceptual design report (CDR) that defines the scope of the facility and the user-access model;
- End station and beam specification to support a staged *in-vitro* biomedical research programme; and
- After comparison and evaluation of three options (LhARA, synchrotron, linac) decide on the technology to be taken forward for the realisation of the facility.

The decision to develop LhARA to serve the ITRF was documented in the 18-month report. The ITRF/LhARA CDR is now being prepared and will address each of the objectives for PA1 listed above.

In the summer of 2023, 9 months into PA1, the collaboration was encouraged to submit a proposal for a second Preliminary Activity (PA2). The PA2 proposal defined a 4-year programme to be delivered over 5 financial years that would deliver:

- Technical Design Reports for the staged implementation of the facility;
- A site study leading to site selection and a building implementation plan; and
- A proof-of-principle demonstrator system at an existing pulsed-laser facility.

The STFC Visions Team ranked proposal “High priority”, however, following peer review, STFC decided not to submit it to the UKRI Infrastructure Committee. While noting that the ambitious ITRF/LhARA proposal had high impact potential and had the potential to drive a step-change in technical capability, the reviewers were concerned regarding the fit to the international landscape and the potential for engagement with the target community.

The work in BP1 will build on the work carried out under the ITRF PA1 and address the issues raised in the peer review. Therefore, the goals for BP1 are to:

- Develop a proof-of-principle laser-driven radiobiology experiment (PoPLaR) on SCAPA at the University of Strathclyde as part of a radiobiology programme that exploits the novel techniques to be employed in LhARA; and
- Initiate the programme required to mitigate the principal risks in the development of LhARA to serve the ITRF: the laser-driven source, Gabor-lens capture, and fixed-field accelerator (FFA).

BP1 will be managed through three work packages:

Work package A: Radiobiology programme;
Work package B: Initial ITRF/LhARA risk-mitigation programme; and
Work package C: Project management, outreach and engagement.

1 Work package details

1.A Work package A: Radiobiological science and technology

Work package managers: J. Parsons, R. Amos

Work package A (WPA) will:

- Develop and execute a programme of radiation biology that incrementally deploys novel technologies relevant to ITRF/LhARA;
- Develop novel instrumentation and diagnostics for use in the radiation biology programme and to be deployed in LhARA;
- Develop outline functional design specifications for automated *in vitro* and *in vivo* experimentation; and
- Implement the PoPLaR proof of principle experiment on SCAPA at the University of Strathclyde.

Tasks and objectives

Task 7: *Radiobiology experiment and simulation*:

Task leader: J. Parsons

Development and execution of radiation biology programme including the proof-of-principle experiment, PoPLaR on SCAPA facility at Strathclyde University.

Task 4: *Ion-acoustic dose-profile measurement*:

Task leader: J. Bamber

Development of ion-acoustic dose measurement system for integration in PoPLaR.

Task 5: *Novel instrumentation, diagnostics and automated end-station specification*:

Task leader: R. Amos, T. Price

Development of concepts for novel instrumentation and diagnostics to maximise the science that can be delivered using the novel LhARA laser-hybrid source.

Development of design for automated *in vitro* and *in vivo* experimentation. Facilitation of commissioning and test of end-station components.

Task 9: *Implementation of PoPLaR on SCAPA at Strathclyde*:

Task leader: R. Gray

Development of proton source and permanent-magnet quadrupole beamline serving PoPLaR.

Milestones

M7.1: Develop beamline and bespoke facilities at SCAPA for radiobiology experimentation; M30:

We will develop the beamline at SCAPA to enable irradiation of well characterised cell lines, which will include establishing a staging system to hold the appropriate cell holders (bespoke glass rings) and to enable medium throughput irradiations. Appropriate radiobiological capabilities (e.g. biological safety cabinets, CO2 incubators, microscopes) will also be established in close proximity to the beamline.

M7.2: Preliminary results from cell survival experiments at SCAPA; M36:

Preliminary experiments will be performed to analyse the survival of well characterised tumour cell lines to laser-accelerated protons at SCAPA at different dose rates (including FLASH). These experiments and setup will be optimised to enable accurate and reproducible survival measurements to be made.

M7.3: Preliminary results from DNA damage and repair experiments at SCAPA; M39:
Preliminary experiments will be performed to analyse the levels of DNA damage and kinetics of repair (using immunofluorescence microscopy and comet assays) in well characterised tumour cell lines following laser-accelerated protons at SCAPA at different dose rates (including FLASH). We will establish the experimental conditions and setup needed to enable more routine and reproducible DNA damage assessments to be made.

M7.4: Assessment of cell survival analysis (RBE's) of laser-accelerated protons; M48:
We will establish survival rates (RBE's) of well characterised tumour cell lines following laser-accelerated protons at SCAPA at different dose rates (including FLASH). These will be comparatively analysed against pre-existing data using cyclotron-accelerated protons (and X-rays) in Birmingham to discover any novel radiobiological differences.

M7.5: Assessment of levels of DNA damage and kinetics of repair of laser-accelerated protons; M48:
We will acquire data analysing the levels of DNA single and double strand break damage (directly or using surrogate markers) and the kinetics of their repair in well characterised tumour cell lines following laser-accelerated protons at SCAPA at different dose rates (including FLASH). These will be correlated with survival analysis, but also comparatively analysed against pre-existing data using cyclotron-accelerated protons (and X-rays) in Birmingham.

M2A.1: Demonstration of beam delivery to end station; M36:
We will install a series of quadrupole magnets into the existing target chamber at the SCAPA laser facility, and integrate them with the laser driven proton source. We will demonstrate the transport of the proton beam and measure the beam properties at the end station, supported by numerical simulations.

M4.3: Design for ion-acoustic dose-profile measurement for PoPLaR; M42

M4.5: LhARA ion-acoustic test results on PoPLaR; M48

M5.4: Deliver PoPLaR end-station; M33:
Construct an end-station compatible with the MC40 cyclotron at the University of Birmingham and SCAPA for the PoPLaR experiments. It will automate the movement of cell dishes using a custom stepping motor and cell dish holder designed for conventional 35mm cell dishes as well as 20mm diameter glass rings with Kapton bases. Relevant additional beam monitors such as film holders, and ionisation chamber holders for dosimetry will also be included.

M5.6: Report on LhARA stage 1 beam monitoring system; M48:
The report will build on the comprehensive literature review from PA1. We will report on the status of the gas jet profiler for measurements of proton beams at SCAPA as well as radiochromic films and novel detector systems identified and tested during the bridging funding.

Resources

Gantt chart and principal milestones

1.B Work package B: ITRF/LhARA risk mitigation

Work package managers: One, Two

Work package B (WPB) will:

- Demonstrate laser generation of protons and ions at energies relevant to LhARA;
- Through experiment and simulation, develop a conceptual design for a prototype Gabor lens appropriate for construction in the period of pre-construction R&D that will follow the Bridging Period; and

- Develop a self-consistent conceptual design for the FFA post accelerator that will form the basis of LhARA Stage 2 so that appropriate prototypes can be constructed in the pre-construction R&D period that will follow the Bridging Period.

Milestones

M2.3: Investigation and demonstration of 10 Hz debris and damage challenges at ICL; M36:

Using the Zhi laser at Imperial College London, we will demonstrate a laser driven ion source running at a repetition rate of 10 Hz, matched to the envisioned ITRF facility. Although the source will be generating proton beams with a lower maximum energy than required by the ITRF, we will be able to utilise the setup to perform studies of debris generation and damage to laser beamline optics and other sensitive components critical to the laser source.

M2.4: Assessment of beam performance during PoPLaR experiment on SCAPA; M48:
We will diagnose and monitor the performance of the laser driven ion source while providing the beam for the PoPLaR experiment, and determine beam stability and integrated system operation. This will aid in developing facility specifications and operational procedures to inform the design of the ITRF.

M3.3: Progress report on performance of increased voltage Penning trap operation and simulation; M36:

M3.4: Final report higher voltage Penning trap operation; M48

M6.2: Final review of R&D work M42

Resources

Gantt chart and principal milestones

1.C Work package C: Project management, outreach and engagement

Work package managers: C. Pugh, C. Whyte

Work package C (WPC) will:

- Organise fortnightly Project Management Board meetings;
- Report as required to ITRF Mamagement on project progress by work package, evolution of the register register and spend; and
- Develop stakeholder and peer-group outreach and engagement, patient and public involvement.

Milestones

D5: Initial PoPLaR and LhARA de-risk update; M30

D6: Interim PoPLaR and LhARA de-risk update; M36

D7: Final PoPLaR and LhARA de-risk update; M42

D8: PoPLaR and LhARA de-risk report; M48

M8.1: Creation of collaborative international clinical research group M40

1. Launch of LhARA: Delivery of a launch event to inform stakeholders, potential users, and the public about the project's existence, purpose, and goals; It will provide a platform for networking, collaboration and forming partnerships with relevant industry members, potential collaborators, government and funders;
2. Website Build and Maintenance: Creation and ongoing maintenance of a website for the LhARA project; and
3. Patient Engagement Session: Delivery of a session aimed at involving patients in the project, gathering their insights and feedback. Creation of accessible content: Updating current information to improve accessibility and understanding.

M8.2: Wider public engagement–All party parliamentary group on radiotherapy; M48:

1. Patient Engagement Group programme: Development of a group representative of the patient community to offer their perspectives, preferences and experiences to inform and co-design the delivery of the LhARA project;
2. Content creation and development: working with all stakeholders, planning, creating and distributing high quality content to engage and educate; and
3. Website maintenance: ensuring website remains functional, secure and user-friendly.

Resources

Gantt chart and principal milestones

2 Bridging activity project-management overview

3 Overview of bridging activity project costs

4 Staff effort

References