Laser-hybrid Accelerator for Radiobiological Applications (LhARA)

Conceptual Design Report

The LhARA collaboration

G. Aymar [1], T. Becker [2], S. Boogert [3], M. Borghesi [4], R. Bingham [5,1], C. Brenner [1], P.N. Burrows [6], T. Dascalu [7], O.C. Ettlinger [8], S. Gibson [3], T. Greenshaw [9], S. Gruber [10], D. Gujral [11], C. Hardiman [11], J. Hughes [9], W.G. Jones [7,20], K. Kirkby [12], A. Kurup [7], J-B. Lagrange [1], K. Long [7,1], W. Luk [7], J. Matheson [1], P. McKenna [5,14], R. Mclauchlan [11], Z. Najmudin [8], H.T. Lau [7], J.L. Parsons [9,21], J. Pasternak [7,1], J. Pozimski [7,1], K. Prise [4], M. Puchalska [13], P. Ratoff [14], G. Schettino[15,19], W. Shields [3], S. Smith [16], J. Thomason [1], S. Towe [17], P. Weightman [9], C. Whyte [5,14], R. Xiao [18]

1. *STFC Rutherford Appleton Laboratory, Harwell Oxford, Didcot, OX11 0QX, UK*
2. *Maxeler Technologies Limited, 3 Hammersmith Grove, London W6 0ND, UK*
3. *John Adams Institute, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK*
4. *Queens University Belfast, University Road, Belfast, BT7 1NN, Northern Ireland, UK*
5. *Department of Physics, SUPA, University of Strathclyde, 16 Richmond Street, Glasgow, G1 1XQ, UK*
6. *John Adams Institute, University of Oxford, Denys Wilkinson Building, Keble Road, Oxford OX1 3RH, UK*
7. *Imperial College London, Exhibition Road, London, SW7 2AZ, UK*
8. *John Adams Institute, Imperial College London, Exhibition Road, London, SW7 2AZ, UK*
9. *University of Liverpool, Liverpool L3 9TA, UK*
10. *Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria*
11. *Imperial College NHS Healthcare Trust, The Bays, South Wharf Road, St Mary's Hospital, London W2 1NY, UK*
12. *University of Manchester, Oxford Road, Manchester, M13 9PL, UK*
13. *Technische Universität Wien, Atominstitut, Stadionallee 2, 1020 Vienna, Austria*
14. *Cockcroft Institute, Daresbury Laboratory, Sci-Tech Daresbury, Daresbury, Warrington, WA4 4AD, UK*
15. *National Physical Laboratory, Hampton Road, Teddington, Middlesex, TW11 0LW, UK*
16. *STFC Daresbury Laboratory, Daresbury, Cheshire, WA4 4AD, UK*
17. *Leo Cancer Care, Broadview, Windmill Hill, Hailsham, East Sussex, BN27 4RY, UK*
18. *Corerain Technologies, 14F, Changfu Jinmao Building (CFC), Trade-free Zone, Futian District, Shenzhen, Guangdong, China*
19. *University of Surrey, 388 Stag Hill, Guilford, GU2 7XH, UK*
20. *Imperial Patient and Public Involvement Group (IPPIG), Imperial College London, Exhibition Road, London, SW7 2AZ, UK*
21. *The Clatterbridge Cancer Centre, Bebington, CH63 4JY, UK*

† *Corresponding author, Email: a.kurup@imperial.ac.uk*

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Executive summary

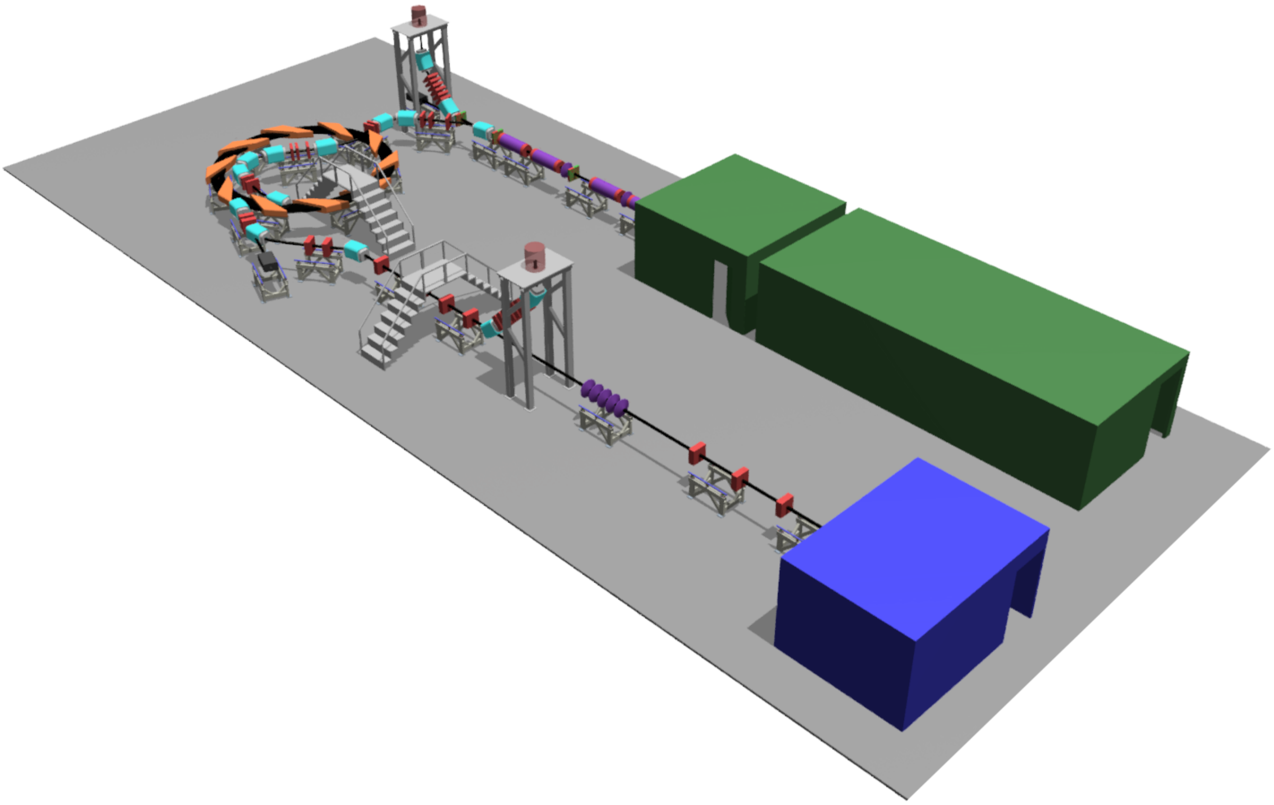

Figure 1: LhARA—the Laser-hybrid Accelerator for Radiobiological Applications.

Cancer is the second most common cause of death globally [1]. In 2018, 18.1 million new cancer cases were diagnosed, 9.6 million people died of cancer-related disease, and 43.8 million people were living with cancer [2, 3]. It is estimated that 26.9 million life-years could be saved in low- and middle-income countries (LMIC) if radiotherapy capacity could be scaled up [4]. Novel techniques incorporated in facilities that are at once robust, automated, efficient, and cost-effective are required to deliver the required scale-up in provision.

Radiation therapy (RT), a cornerstone of cancer treatment, is used in over 50% of cancer patients [5]. The most frequently used types of radiotherapy employ photon or electron beams with MeV-scale energies. Proton and ion beams offer substantial advantages over X-rays because the bulk of the beam energy is deposited in the Bragg peak. This allows dose to be conformed to the tumour while sparing healthy tissue and organs at risk.

The benefits of proton and ion-beam therapy (PBT) are widely recognised. There are approximately 88 PBT centres worldwide, and at least 40 under construction [6]. PBT today is routinely delivered in fractions of ~ 2 Gy per day over several weeks. Usually, each fraction is delivered at a low dose rate (< 10 Gy/min) deposited uniformly over the target treatment volume. Exciting evidence of therapeutic benefit has recently been reported when dose is delivered at ultra-high dose-rate, $\gtrsim 40$ Gy/s ("FLASH" RT) [7, 8], or provided in multiple micro-beams with diameter less than 1 mm distributed over a grid with inter-beam spacing of ~ 3 mm [9]. However, the radiobiological mechanisms by which the therapeutic benefit is generated are not properly understood.

LhARA, the Laser-hybrid Accelerator for Radiobiological Applications, is conceived as the new, highly flexible, source of radiation that is required to explore the vast "terra incognita" of the mechanisms by which the biological response to ionising radiation is determined by the physical characteristics of the beam [10]. The LhARA collaboration's concept, shown in figure 1, is to exploit a laser to drive the creation of a large flux of protons or light ions which are captured and formed into a beam by strong-focusing plasma lenses. The laser-driven source allows protons and ions to be captured at energies significantly above the proton- and ion-capture energies that pertain in conventional facilities, thereby evading the current space-charge limit on the instantaneous dose rate that can be delivered [11]. The plasma (Gabor) lenses provide the same focusing strength as high-field solenoids at a fraction of the cost. Post-acceleration, performed using a fixed field alternating gradient accelerator (FFA), will preserve the unique flexibility in the time, energy, and spatial structure of the beam afforded by the laser-driven source.

We propose that LhARA be developed in two stages. In the first stage, the laser-driven beam, captured and transported using plasma lenses and bending magnets, will serve a programme of in-vitro experiments with proton beams of energy of up to 15 MeV. In stage two, the beam will be accelerated using an FFA. This will allow experiments to be carried out in vitro and in vivo with proton-beam energies of up to 125 MeV. Ion beams (including C^{6+}) with energies up to 30 MeV per nucleon will also be available. Figure 2 compares the energy and estimated maximum instantaneous dose rate of LhARA to the performance of other clinical and laboratory facilities that provide, or plan to provide, proton and ion beams for radiobiology. The beam energy at LhARA has been specified to allow in-vitro experiments and in-vivo studies using small mammals. The LhARA collaboration's hybrid approach will allow the unique properties of the laser-driven source—extremely high instantaneous flux in an extremely sort pulse over a tiny area—to be preserved and exploited to deliver radiobiological investigations in completely new regimes.

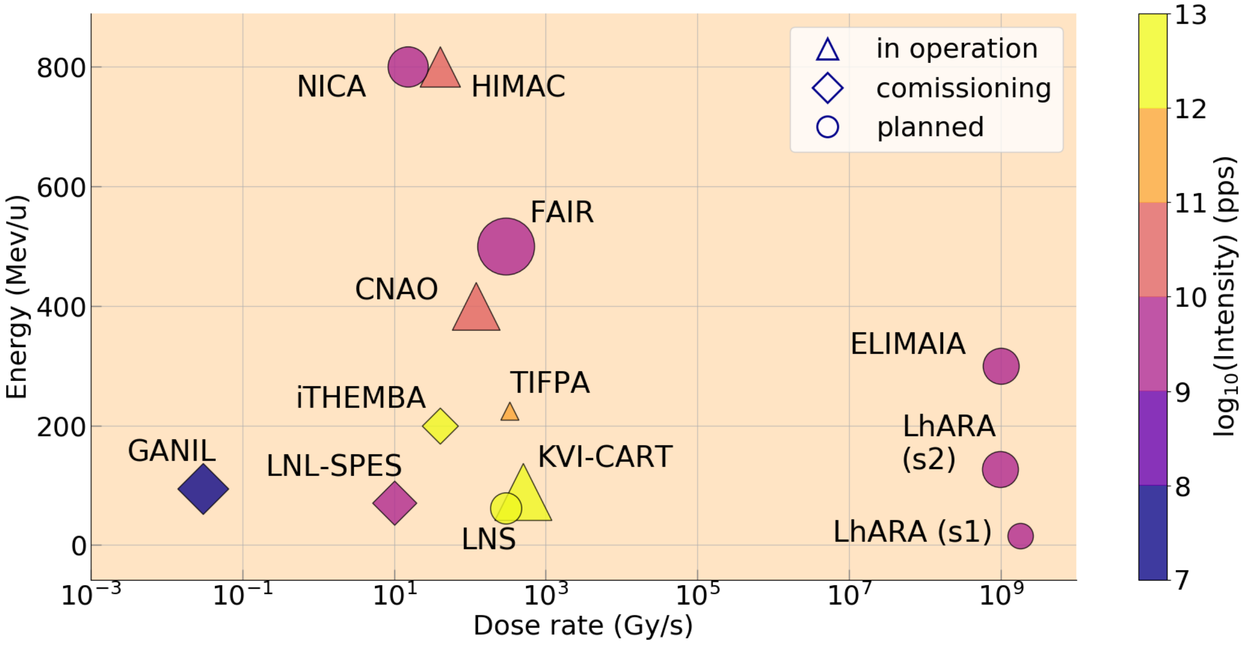

Figure 2: Comparison of the projected performance of LhARA at Stage 1 (S1) and Stage 2 (S2) with the performance of other facilities that provide, or plan to provide, beams for radiobiology [12–30]. The energy of the beam provided is plotted against the maximum instantaneous dose. The range of ion species that are provided by the facility is indicated by the relative size of the marker.

LhARA will not be developed or operate in isolation. Proton and ion beams for radiobiological research are available at a number of laboratories in Europe, the Americas, Africa, and in Asia. A number of clinical proton- and ion-beam centres (e.g. [22, 24]) also provide beams for research. Beam time for radiobiology at research laboratories is often restricted by the pressure of other users while time to do research at clinical facilities is limited by the demands of patient treatment. A small number of laboratories in Europe actively seek to develop laser-driven sources for biomedical applications (e.g. [21]). The LhARA collaboration's vision is to build on this work to demonstrate the feasibility of capturing and manipulating the flux created in the laser-target interaction to provide a beam that can be accelerated rapidly to the desired energy.

The laser pulse that initiates the production of protons or ions at LhARA may be triggered at a repetition rate of up to 10 Hz. The time structure of the beam may therefore be varied to interrupt the chemical and biological pathways that determine the biological response to ionising radiation with 10 ns to 40 ns long proton or ion bunches repeated at intervals as small as 100 ms. The technologies chosen to capture, transport, and accelerate the beam in LhARA have been made so that this unique capability is preserved. The LhARA beam may be used to deliver an almost uniform dose distribution over a circular area with a maximum diameter of between 1 cm and 3 cm. Alternatively the beam can be focused to a spot with diameter of $\sim$ 1 mm. The key features of LhARA for the study of radiobiology will be:

- *Flexibility*: to provide a wide variety of temporal, spectral, and spatial beam structures to enable exhaustive investigation of the impact of beam parameters on the micro-biophysical processes that determine the response of living tissue to ionising radiation.
- *Low beam divergence*: as it enters the in-vitro and the in-vivo end-stations is a feature of the optical design of the facility. This will be an important advantage in the study of spatially fractionated radiotherapy.
- *Multiple ion species*: will be provided over a variety of temporal and spatial distributions in a single facility to allow direct comparison of the radiobiological impact of the different species and provide a means to assess their relative benefits for therapy.
- *Availability*: the specification of the laser-driven source has been made to allow the dose delivered to the biological samples to be accurate and reproducible. This, combined with the fact that LhARA will be a facility dedicated to the study of radiobiology will allow the assessment of temporal and spatial fractionation schemes in combination with immunotherapy and chemotherapy and the evaluation of the relative biological effectiveness using complex endpoints such as angiogenesis, inflammation etc.

The development of LhARA will drive advances in technique with application well beyond the study of radiobiology. By establishing LhARA, the research programme will:

- Prove the feasibility of the laser-hybrid technique, evading the instantaneous flux limit imposed by the space-charge effect in current proton and ion sources;
- Demonstrate that electron-plasma lenses are a viable alternative to high-field solenoids for the capture and transport of proton and ion beams;
- Demonstrate through operation that a fixed field alternating gradient accelerator with variable extraction energy is capable of the routine acceleration of proton and ion beams in a production facility; and
- Integrate real-time dose-deposition imaging in a fast feedback and control system to demonstrate the reproducible delivery of dose using a laser-hybrid accelerator system.

The technologies demonstrated in LhARA have the potential to be developed to make "best in class" treatments available to the many by reducing the footprint of future particle-beam therapy systems. The laser-hybrid approach, therefore, will allow radiobiological studies and eventually radiotherapy to be carried out in completely new regimes, delivering a variety of ion species in a broad range of time structures and spatial configurations at instantaneous dose rates up to and potentially significantly beyond the current ultra-high dose-rate "FLASH" regime.

The LhARA consortium is the multidisciplinary collaboration of clinical oncologists, medical and academic physicists, biologists, engineers, and industrialists required to deliver such a transformative particle-beam system. With this "pre Conceptual Design Report" (pre-CDR) we seek to lay out our concept for LhARA, its potential to serve a ground-breaking programme of radiobiology, and the technological advances that will be made in its execution. The work presented in the LhARA pre-CDR lays the foundations for the development of full conceptual and technical designs for the facility. The pre-CDR also contains a description of the R&D that is required to demonstrate the feasibility of critical components and systems. An initial cost and schedule exercise has been carried out. This analysis shows that the first radiobiological experiments could be carried out within five years of the start of the LhARA project if appropriate resources can be secured.

Lay summary

For many years the delivery of radiotherapy in the treatment of cancer has involved directing a beam of high-energy photons (X-rays) at cancer tumours, to kill the cancer cells. This has proved to be a very successful treatment for many cancers. However, it has the disadvantage that the photons in the beam not only kill cells in the tumour but also damage cells in the healthy tissue through which the the beam passes. Further damage can occur outside the beam because the photons can scatter as they pass through the patient. To reduce the severity of these unwanted effects requires that the X-ray dose delivered to the tumour is limited to avoid giving too high a dose to healthy tissues. Damage to healthy tissue can further be reduced by concentrating the photons on the tumour using beams directed from different angles, in a kind of cross-fire. This is achieved by rotating the source of the photons around the patient.

More recently a different type of radiotherapy "proton beam radiotherapy" has been developed. In this form of treatment a beam of high-energy protons (rather than photons) is directed at the tumour. The main advantage of using beams of protons is that they cause very little damage until they come to the end of their range at which point they deliver an enhanced dose by ionising atoms in a very small volume. The energy of the proton beams can be adjusted so that they stop within the tumour. This has the advantage that very little damage is done to the healthy tissue outside the tumour. Such proton machines need a very large and expensive proton accelerator to produce the beam, so there are very few of them in most countries. Moreover, because they are extremely large it is difficult to vary the angle of the beam (which is sometimes necessary) and also difficult to ensure that the proton beam stops exactly where required in the body.

Research shows that there is a significant advantage in delivering the protons as a series high intensity bunches and also in the form of several very narrow closely-spaced "micro beams". Other investigations underway at present involve the use of ions heavier than protons such as helium or carbon. These are exciting developments as they point to more effective destruction of cancer cells whilst also reducing damage to healthy cells. However, they also highlight the need to improve our understanding of the basic mechanisms by which protons and heavy ions generate biological impact. Thus, the most important aim of LhARA is to pursue this radiobiology research in new regimes to inform and help develop better treatments. The other aspect of LhARA is technological research to replace the large and expensive proton accelerator with a high-powered laser-based accelerator. This would prove to be more flexible, less expensive and better able to produce the very short intense pulses needed.

To summarise, the LhARA proposal is a crucial first step in a full R&D programme to transform proton beam therapy by enabling more effective higher doses to be given safely and accurately. It will also significantly benefit cancer patients by reducing their course of radiotherapy treatment to days rather than several weeks, as well as almost eliminating the risk of damage to the healthy tissue that surrounds the tumour. This requires (a) scientific research to explore radiobiology in new regimes and (b) research into the physics and technology of laser-hybrid proton accelerators in order to produce new machines.

W.G. Jones on behalf of the Imperial Patient and Public Involvement Group (IPPIG).

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