# Advanced technologies for radiobiology and clinical radiotherapy

## 1 Project description and objectives

Laser-driven proton and ion sources are disruptive technologies that offer enormous potential to satisfy the anticipated growth in demand for particle-beam therapy (PBT). A laser-hybrid system, in which strong-focusing plasma lenses capture and transport the beam, will allow clinicians to deliver PBT in a completely new regimen, combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates (up to $10^9$ Gy/s [1] compared to conventional dose rates of the order of a Gy/s).

We have created a multidisciplinary collaboration of clinical oncologists, medical, particle, plasma and laser physicists, accelerator and instrumentation scientists, and radiobiologists that has the ambition to: improve the efficacy of PBT by increasing our in-depth understanding of the biological effect of charged-particle beams; and make 'best in class' treatments available to the many by reducing the footprint of future PBT systems such that a larger number of centres can be implemented across the country.

Our approach is aligned with that of the international Biophysics Collaboration (IBC) that was established on the 22$^{\text{nd}}$ May 2019 at the collaboration's first meeting which was held at GSI, Darmstadt, Germany [2] of which Imperial's new Centre for the Clinical Application of Particles (the CCAP [3]) is a founder member.

With this proposal we seek the resources to:

1. Deliver an outline CDR for the 'Laser-hybrid Accelerator for Radiobiological Applications', LhARA;
2. Establish a test-bed for advanced technologies for radiobiology and clinical radiotherapy at the Clatterbridge Cancer Centre (CCC); and
3. Create a broad, multi-disciplinary UK coalition, working within the IBC to place the UK in pole position to contribute to and to benefit from this exciting new biomedical science-and-innovation initiative.

## 2 Scientific justification

***Overarching vision:***

The instantaneous dose rate that can be delivered by PBT facilities today is limited at the ion source by the space-charge effect. We propose to evade this limitation by developing a novel hybrid accelerator in which laser interactions create a large flux of protons or light ions which are captured and formed into a beam in a series of strong-focusing plasma lenses. The hybrid approach harnesses the unique properties of the laser-driven source: delivery of a range of ion species ($p$ to $C^{6+}$) from a single source in ultra-short pulses that each deliver an enormous instantaneous dose. The successful demonstration of efficient capture and cylindrically-symmetric electrostatic focusing will be an important step towards the exploitation of laser-driven beams.

We propose that LhARA [4, 5] 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 $\sim$ 15 MeV. In stage two, the beam will be accelerated using a fixed-field accelerator (FFA) with a large dynamic aperture. This will allow experiments to be carried out *in vitro* and *in vivo* with proton-beam energies of $\lesssim 125$ MeV. Ion beams (including $C^{6+}$) with energies up to $\sim$ 30 MeV per nucleon will also be available for experimentation. Our vision is that the integration of the techniques that we shall develop in this novel system for radiobiology will prove the feasibility of the laser-driven hybrid-accelerator approach, thereby laying the technological foundations of the programme required to transform the delivery of PBT while delivering a world-class radiobiology programme.

***Motivation for the decision to target delivery of a radiobiological system:***

Radiotherapy is used to treat approximately 50% of all cancer patients. Proton and ion beams offer substantial advantages over X-rays in the treatment of cancer 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. As a consequence there has been an increase in the use and development of PBT worldwide [6].

The efficacy of proton and ion beams is characterised by their 'relative biological effectiveness' (RBE) in comparison to reference photon beams. It is known that RBE depends strongly on many factors, including particle energy, dose, dose rate, and tissue type but the radiobiology that determines these dependencies is not fully understood [7]. Our recent studies have identified vital roles for specific proteins and mechanisms involved in the signalling and processing of DNA damage and repair as critical factors in the cellular response to protons [8, 9]. These results indicate that a systematic programme of radiobiology is vital for a full understanding of the bio-physical processes that are induced by ionising radiation in tissue to be developed. This understanding can then be exploited to maximise the efficacy of PBT now and in the future.

## 3 Awareness and context

***LhARA's uniquely flexible capabilities in comparison to facilities serving radiobiology today:***

There are approximately 70 PBT centres worldwide, and at least 40 under construction [10]. The PBT facility at the Christie Hospital is in operation and the University College London Hospital centre is scheduled to open in 2020. Patient treatment is the principal function of each of these facilities. A privately-funded PBT accelerator test facility is to be established at the Daresbury Laboratory.

While a research beam line is currently being developed at the Christie Hospital, beam-time will be restricted. In addition, the beam properties limit the range of radiobiological experiment that can be performed. The CCC uses a 60 MeV proton beam for eye-tumour treatment and also serves to deliver a radiobiology research programme. We propose to upgrade an existing beam-line at Clatterbridge to deliver proton beams to enhance radiobiology capabilities and to serve as a test-bed for the advanced techniques that we propose to develop. Recent studies have demonstrated the use of ultra-high dose rate, 'FLASH', irradiation for protection of normal tissues [11, 12]. Therefore, the capability to deliver an instantaneous dose rate significantly in excess of that available clinically will be included in the upgrade programme. In this way, the LhARA team will have early access to a facility dedicated to the development of advanced techniques for radiobiology, including preliminary investigation of ultra-high dose rate 'FLASH' irradiation with protons.

***The unique advantages of the laser-hybrid approach:***

Beam is extracted at fixed energy from conventional cyclotrons such as those in use at PBT centres in the UK. The dose rate can be varied by adjusting the bunch intensity and the pulse length at the ion source. However the instantaneous dose rate is limited by source brightness, losses at injection, bunch length, and losses during acceleration and extraction. A reasonable estimate of the maximum bunch intensity that can be achieved is approximately $1.2 \times 10^7$ protons per bunch. In order to vary the beam energy a degrader is used to intercept the beam after extraction. Multiple Coulomb scattering and energy straggling cause a significant reduction in beam quality. This can be recovered through collimation with an unavoidable loss in beam intensity. Changing the extraction energy is possible, but is extremely difficult as even a small change in magnet saturation strongly affects the isochronous acceleration. Variable-energy extraction achieved by varying stripper-foil position is possible for $H^-$ ions. However, the application of this technique to multiple ion species is challenging and is likely to require multiple extraction ports leading to issues in commissioning and operation. The acceleration of more than one ion species is possible by harmonic operation and tuning of the magnetic field, but is limited to ions with specific charge-to-mass ratios and cannot accommodate a full ion spectrum.

Conventional synchrotrons, such as that used at MedAustron, can deliver beam over a range of energies. The dose delivered is controlled through the process of slow extraction which takes place over a period of around 1 s. The instantaneous intensity that can be achieved within a time window equivalent to the cyclotron bunch length considered above is approximately $4 \times 10^8$ protons per pulse. The MedAustron synchrotron has two ion sources, the first delivers $H_3^+$ ions, the second $C^{4+}$ ions. These ions have the same charge-to-mass ratio and, after short,

ion-specific transfer lines, are injected into a single radiofrequency quadruple (RFQ). Electrons are stripped from the ions at injection. The use of other types of ion with the same charge/mass is possible in principle.

LhARA is a compact, cost-effective solution for the delivery of proton and ion beams over a range of energy, dose-rate and ion species. The intensity of the bunch is varied by changing the laser-beam parameters. The dose can be delivered in a single 10 ns bunch with an intensity of $\gtrsim 10^9$ protons per pulse or over 600 bunches at 10 Hz repetition rate. The energy can be varied by collimating the beam delivered by the very strong energy-dependent electrostatic focusing provided by the plasma lenses. Beam can be extracted from the FFA post accelerator over a range of energy using methods established by the RACCAM and PAMELA projects [13–17]. Almost any type of ion can be accelerated in LhARA simply by changing the target. LhARA has the potential to become a uniquely flexible source for radiobiology and a catalyst for the development of laser-hybrid solutions for PBT and other scientific and technological applications.

***Complementary initiatives to create laser-driven beams for radiobiology:***

Laser-driven ions have been posited as a source for radiobiological studies for a number of years [1, 18–35]. However, to date the ion energies, energy spread, and shot-to-shot variability of the flux produced has meant that such sources were not suitable to serve as a radiobiology resource. A number of radiobiology experiments have been conducted with laser-accelerated ions, but these have been limited in scope to single-shot illumination, either due to low laser repetition rates or the lack of a target suitable for operation at high repetition rate. Most of these experiments have been performed on facilities for which radiobiology has not been the highest priority. The UK has been a pioneer in the study of laser-accelerated ions for hadron therapy. Currently the A-SAIL collaboration [36], within which CCAP members play a pivotal role, is exploring the underlying fundamental physics required to produce the proton and ion beams we require. The programme we propose will continue to benefit from the advances made in the UK and overseas.

European laboratories are active in the development of laser-driven sources for PBT. A number of groups are investigating the challenges related to the production and capture of ion beams with the desired characteristics. In Germany, the effort is led by the Helmholtz Zentrum Dresden-Rosendorf (HZDR), the Technical University of Munich, and GSI Helmholtzzentrum für Schwerionenforschung (GSI). Primary experiments are also now beginning at the ELIMAIA-ELIMED facility in the Czech Republic. The ELIMED project, a multi-billion euro collaboration to build and exploit next generation laser sources, has a dedicated programme for radiobiology research based on a laser-accelerated source. This project has close collaborations with researchers from a number of institutes in Italy. At the J-KAREN-P facility in Japan, with which CCAP members have an ongoing collaboration, the focus is on developing carbon ions for particle treatment.

The initiatives outlined above exploit conventional magnetic quadrupole or solenoid focusing to capture and transport the laser-generated beam. The capture and transport efficiency of the plasma-lens-based solution we propose is superior and we therefore expect to be able to deliver beams with a substantially higher instantaneous dose. To preserve the unique advantages of the laser-driven ion source we propose to us an FFA that provides fast acceleration with large dynamic aperture.

## 4 Research methodology

1. Complete an end-to-end simulation of LhARA. The results will be presented in the initial LhARA CDR and lead to a variety of proposals to take the programme forward;
2. Support CCC personnel in the beam-line refurbishment to create a test facility for radiobiological measurement, particularly using FLASH, and testing of prototype equipment; and
3. Forge the UK coalition that will contribute to the IBC. Through targeted national and international meetings and networking events we will contribute to the development of the collaboration's scientific programme and place the UK at the heart of the activity.

## 5 Potential for Societal and Economic Impact

We propose to prove the principle of the laser-hybrid accelerator scheme in a production radiobiology facility. Our proof-of-principle system has the potential to be scaled up to deliver a step change in clinical capability. Other applications of high-power pulsed proton and ion beams also have the potential to benefit from the removal of the space-charge limit in instantaneous beam intensity.

Ultimately these technological advances, combined with the measurement programme LhARA will serve, will lead to the discovery of optimal PBT strategies thereby delivering a significant societal impact. By engaging appropriately with industrial partners from the outset we seek to position the UK to generate substantial economic gains through the industrialisation of the novel techniques we shall develop.

## 6 Applicant track record

K. Long (Imperial) is the inaugural Director of the CCAP and international MICE spokesperson. He has extensive project leadership experience. Each of the other CoIs from Imperial are leading academics spanning the fields of accelerator science, detector development, scientific computing, and machine learning.

J. Parsons (Liverpool) has significant expertise in the biochemistry, molecular and cellular biology of ionising radiation-induced DNA damage and repair, with a more recent focus on PBT ($> 50$ peer-reviewed publications; H-Index:26). He is also the lead for radiobiology research at the CCC and the University of Liverpool.

## 7 Project Management and Work Plan

*Preparation of initial CDR for LhARA*; work-package manager: K. Long:
The principal contributors to the initial design study will be the two early career researchers supported by this award. The completion of the end-to-end simulation and preparation of the initial CDR will build on work that is already underway within the CCAP.
Milestone: initial CDR ready for journal submission; month 8.
*LhARA and radiobiology test facility*; work-package manager: J. Parsons:
The requested post-doctoral researcher will work with project partners and CCC staff to upgrade the beam-line and perform dosimetry to enable FLASH capabilities. Radiobiology experiments will be initiated.
Milestone: refurbished beam-line commissioning: month 9.
*Forging the UK and international Radiobiology Collaborations*; work-package manager: K. Long:
A series of meetings and networking events will be organised with national and international stakeholders.
Milestone: initial UK community meeting: month 6;
Milestone: presentation of proposed UK contributions at the $2^{\text{nd}}$ IBC meeting: month 24.

## 8 Justification of resources

The resources requested will support two post-doctoral researchers currently in post at Imperial and Liverpool at 100% for 6 months each. The bulk of this staff effort will be expended in the first six months of the award to deliver the initial LhARA CDR. Travel is requested to organise meetings and networking events to build the national and international collaborations. We estimate that we shall require 20 trips of 2–3 days at £350 per trip within the country and 10 international trips of 2–3 days at £1000 per trip within Europe. The total travel request is therefore £18.75k.

## 9 Spend profile statement

It is important that the initial CDR is delivered in the first 6 to 8 months of the award, therefore the two early-career researchers will focus on this as soon as the award is in place. We are therefore confident that the bulk of the resources can be committed before the end of March 2020.

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