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PPRP
PROPOSAL

Document Status: With Council
STFC Reference: ST/T002638/1

Opportunities Call 2019

Organisation where the Grant would be held

Organisation	Imperial College London	Research Organisation Reference:	P82401
Division or Department	Dept of Physics		

Project Title [up to 150 chars]

Advanced concepts and novel technologies for the study of the impact of ionising radiation on tissue

Start Date and Duration

a. Proposed start date	01 October 2019	b. Duration of the grant (months)	24

Applicants

Role	Name	Organisation	Division or Department	How many hours a week will the investigator work on the project?
Principal Investigator	Professor Kenneth Long	Imperial College London	Dept of Physics	3.75
Co-Investigator	Professor David Colling	Imperial College London	Dept of Physics	3.75
Co-Investigator	Dr Jaroslaw Pasternak	Imperial College London	Dept of Physics	3.75
Co-Investigator	Dr Juergen Pozimski	Imperial College London	Dept of Physics	3.75
Co-Investigator	Professor Wayne Luk	Imperial College London	Dept of Computing	3.75
Co-Investigator	Professor Zulfikar Najmudin	Imperial College London	Dept of Physics	3.75
Researcher-Co-Investigator	Dr Ajit Kurup	Imperial College London	Dept of Physics	9.38

Proposal Classifications

Classification Areas:

Research Areas are the subject areas in which the research proposal may fall and you should select at least one of these with a maximum of five allowed. You will need to assign the relative percentage totaling 100% across all areas selected. To add or remove Research Areas use the relevant link below. To set a primary area, click in the corresponding checkbox and then the Set Primary Area button that will appear.

Subject	Topic	Indicator %	Keyword
Particle physics - experiment	Accelerator R&D	75	

Science and Technology Studies	Science and Technology Studies	25	

Qualifiers:

Qualifiers are terms that further describe the area of your research and cover aspects such as approach, time period, and geographical focus. Please ensure you complete this section if relevant. To add or remove Qualifiers use the links below.

Type	**Name**
Approach	Experimental
Approach	Knowledge exchange
Approach	Modelling
Approach	Technique/Method Development
Health categories	Cancer
Health categories	Generic Health Relevance
Health categories	Other

Keywords:

Free-text keywords may be used to describe the subject area of the proposal in more detail. To add or remove those previously added use the links below.

Objectives

List the main objectives of the proposed research in order of priority [up to 4000 chars]

The principal objectives of our research proposal are:

1. CDR for the Laser-hybrid Accelerator for Radiobiological Applications

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 regime, combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates (up to 10^9 Gy/s compared to conventional dose rates of the order of a Gy/s).

The Laser-hybrid Accelerator for Radiobiological Applications (LhARA) is conceived to be built in two stages. In the first stage, the laser-driven beam, captured and transported using strong-focusing plasma lenses and bending magnets, will serve a programme of in-vitro experiments with proton beams of energy ~15 MeV. In the second stage, the beam will be accelerated using a fixed-field accelerator (FFA) with large dynamic aperture to allow experiments to be carried out in vitro and in vivo with proton-beam energies of ~75 MeV. Ion beams (including C{6+}) with energies up to ~20 MeV per nucleon will also be available.

By demonstrating the techniques that we shall develop in a novel system for radiobiology, we 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.

2. Establish a LhARA test-bed at the Clatterbridge Cancer Centre (CCC)

The factors that determine the therapeutic effect of proton and ion beams are not fully understood. A full understanding of the bio-physical processes that are induced by ionising radiation in tissue is essential for the efficacy of PBT to be optimised now and in the future.

We propose to upgrade an existing beam-line at the CCC to deliver proton beams for further radiobiology research and to serve as a test-bed for the advanced techniques that we propose to develop. 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.

3. Create the UK consortium within the international Biophysics Collaboration (iBC) and define its initial scope

The iBC was established on the 22nd May 2019 at the collaboration's first meeting which was held at GSI, Darmstadt, Germany. Imperial's new Centre for the Clinical Application of Particles (the CCAP) is a founder member.

We will reach out across the UK to forge the coalition that wishes to 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. By placing the UK at the heart of the activity we shall have outstanding opportunities to bid collectively and in small groups to national and international sources of funding. The programme will culminate with the second meeting of the iBC where the UK's contributions to the emerging scientific programme of the collaboration will be presented.

Summary

Describe the proposed research in simple terms in a way that could be publicised to a general audience [up to 4000 chars]. Note that this summary will be automatically published on STFC's website in the event that a grant is awarded.

Cancer is the second most common cause of death globally, accounting for 8.8 million deaths in 2015. It is estimated that radiotherapy is used in the treatment of approximately half of all cancer patients. In the UK, one new NHS proton-beam therapy facility has recently come online in Manchester and a second will soon be brought into operation in London. In addition, several new private proton-beam therapy facilities are being developed. The use of these new centres, and the research that will be carried out to enhance the efficacy of the treatments they deliver, will substantially increase demand. Worldwide interest in particle-beam therapy (PBT) is growing and a significant growth in demand in this technology is anticipated. By 2035, 26.9 million life-years in low- and middle-income countries could be saved if radiotherapy capacity could be scaled up. The investment required for this expansion will generate substantial economic gains.

Radiotherapy delivered using X-ray beams or radioactive sources is an established form of treatment widely exploited to treat cancer. Modern X-ray therapy machines allow the dose to be concentrated over the tumour volume. X-ray dose falls exponentially with depth so that the location of primary tumours in relation to heart, lungs, oesophagus and spine limits dose intensity in a significant proportion of cases. The proximity of healthy organs to important primary cancer sites implies a fundamental limit on the photon-dose intensities that may be delivered.

Proton and ion beams lose the bulk of their energy as they come to rest. The energy-loss distribution therefore has a pronounced 'Bragg peak' at the maximum range. Proton and ion beams overcome the fundamental limitation of X-ray therapy because, in comparison to photons, there is little (ions) or no (protons) dose deposited beyond the distal tumour edge. This saves a factor of 2-3 in integrated patient dose. In addition, as the Bragg peak occurs at the maximum range of the beam, treatment can be conformed to the tumour volume.

Protons with energies between 10MeV and 250MeV can be delivered using cyclotrons which can be obtained `off the shelf' from a number of suppliers. Today, cyclotrons are most commonly used for proton-beam therapy. Such machines are not able to deliver multiple ion species over the range of energies required for treatment. Synchrotrons are the second most common type of accelerator used for proton- and ion-beam therapy and are more flexible than cyclotrons in the range of beam energy that can be delivered. However, the footprint, complexity and maintenance requirements are all larger for synchrotrons than for cyclotrons, which increases the necessary investment and the running costs.

We propose to lay the technological foundations for the development of an automated, adaptive system required to deliver personalised proton- and ion-beam therapy by implementing a novel laser-driven hybrid accelerator system dedicated to the study of radiobiology. Over the two years of this programme we will:

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

Academic Beneficiaries

Describe who will benefit from the research [up to 4000 chars]

With this proposal we seek to lay to the foundations of a programme to develop a laser-hybrid accelerator that exploits novel, strong-focusing, plasma-lens technology to commission a flexible source capable of delivering a variety of ions over a broad range of energy and which is capable of delivering extremely high instantaneous dose rates. By demonstrating that our system can evade the space-charge limitations of current ion sources, we shall have created a new source for high-power beams and demonstrated the successful exploitation of laser-hybrid acceleration for production applications in science and innovation. Our results will therefore be of interest to the accelerator science community as well as those who develop or exploit high power beams for science and/or innovation.

By enhancing the capability of the Clatterbridge Cancer Centre to support further radiobiological research we shall create a test-bed for the development of advanced technologies and a vehicle for the study of the radiobiological effects of protons using in vitro and in vivo models. This area of research will therefore be of benefit to academics in the radiobiology and DNA-damage response fields, particularly those with an interest in the molecular and cellular mechanisms of particle beam therapy (PBT)-induced DNA damage and repair.

We also seek to forge a UK coalition involving clinical oncologists, medical, particle, plasma and laser physicists, accelerator and instrumentation scientists, and radiobiologists who seek to contribute to, and to benefit from, the work of the international Biophysics Collaboration. This is a substantial opportunity and will be of benefit to physicists and clinicians with an interest in the interactions of PBT with molecules and cells, linked to a specific biological end-point (e.g. DNA damage, cell death), as well as those with an interest in clinical oncology in general.

We will ensure that the results of our research are made available to the academic community at large through open-access peer-reviewed publications and presentations at national and international scientific conferences, so that all academic beneficiaries are reached and so that our collaboration will have the potential to secure further collaborative research income. Given the significant increase in PBT centres worldwide, and particularly in the UK, the work we propose to carry out is vital as the radiobiology of PBT is not fully understood and an increase in knowledge is required ultimately to deliver optimal strategies for effective treatment of specific cancers.

Our proposal involves and is supported by a multidisciplinary collaboration of clinical oncologists, medical, particle, plasma and laser physicists, accelerator and instrumentation scientists, radiobiologists, and industrialists. This multi-disciplinary collaborations the core of the strong UK-based coalition that we propose to establish to drive forward a far-reaching PBT radiobiological programme that is likely to benefit not only the academic community, but also to have a significant impact on biomedicine, society and to generate substantial economic benefits.

Impact Summary

Impact Summary (please refer to the help for guidance on what to consider when completing this section) [up to 4000 chars]

The long-term objective of the research programme is to transform the delivery of proton- and ion-beam therapy using a system that is:

* Automated and is capable of adjusting the dose delivered in real time based on measurements of the position of the patient, tumour, organs at risk, and the dose-deposition profile;
* Capable of delivering a range of ion species from protons to carbon ions over a wide variety of dose rates, up to and including those required for FLASH radiotherapy, in the same treatment session; and
* Has a footprint small enough that provision of the therapy can be distributed across the country.

The societal benefits of the substantial increase in access to advanced proton- and ion-beam therapy for effective cancer treatment that would result from the successful execution of this programme is clear.

To lay the foundations of the technological programme required to deliver the outcomes outlined above we have formed an multidisciplinary collaboration composed of clinical oncologists, medical and academic physicists, biologists, engineers, and industrialists. We propose to take a holisitic `system' approach to the delivery of the programme. This requires that various technological developments required to implement a full system are brought forward in parallel. The creation of a project team that has the diverse skill set and motivation to take the project forward to deliver the long-term goal is a clear priority. Further, the sustainable development of the programme from proof of concept to spin out will require staff with a breadth of experience across the disciplines. The series of meetings and networking events that will be scheduled as part of our programme will be used to further enhance the collaborative network which will deliver our overall aims and goals.

We will prove the principle of the laser-hybrid accelerator system within a facility dedicated to radiobiology research. This facility will enable further characterisation of the radiobiological effects of proton and ion beams, particularly at the molecular and cellular level, leading to a significant scientific impact. Specifically the collaborative team has expertise in

examining the impact of ionising radiation on cell survival in different tumour models linked with effects on DNA damage and repair, which will be used to deliver the current proposal for increased scientific knowledge and gain. Overall, our proof-of-principle system has the potential to deliver a step up in clinical capability by improving the delivery and efficacy of particle-beam therapy for the benefit of cancer patients. As well as the societal impact that this will achieve, we will engage with industrial partners to place the UK in a unique position to generate substantial economic gains through the industrialisation of the novel techniques that this proposal will develop.

Pathways to Impact

Overview

Academic excellence across our multidisciplinary collaboration is at the forefront of our mission. In achieving this we will open the doors for a correspondingly high-level of societal and economic impact.

We seek to lay the foundations of a programme that will drive a paradigm shift in the provision of laser-hybrid accelerator systems for biomedical applications. Our approach is to forge a collaboration that will specify and design proton and ion accelerators for use in radiobiological experiments. A hands-on accelerator R&D and radiobiology measurement programme will accompany the design work. Our intention is to prepare for the construction of prototype facilities. The work of the design-study work package will position the consortium to take the lead in the future development laser-hybrid facilities; the development of a radiobiological measurement and test facility at the Clatterbridge Caner Centre with ultra-high dose-rate capability will similarly position the UK consortium at the forefront of the field. Embedding the R&D activity within the context of the emerging International Biophysics Collaboration gives enormous opportunities to bid successfully for follow-on funding.

Societal impact

The long-term objective of our research programme is to transform the delivery of proton- and ion-beam therapy using a system that is:

- Automated and is capable of adjusting the dose delivered in real time based on measurements of the position of patient, tumour, organs at risk, and the dose-deposition profile;
- Capable of delivering a range of ion species from proton to carbon over a wide variety of dose rates, up to and including those required for FLASH radiotherapy, in the same treatment session; and
- Has a footprint small enough that provision of the therapy can be distributed across the country.

The societal benefits of the substantial increase in access to advanced proton- and ion-beam therapy that would result from the successful executionof this programme, particularly in terms of delivering optimal cancer treatment, is clear.

To lay the foundations of the technology required to deliver the programme outlined above, we have formed an multidisciplinary collaboration composed of clinical oncologists, medical and academic physicists, biologists, engineers, and industrialists. We propose to take a holisitic `system' approach to the delivery of the programme. This requires that various technological developments required to implement a full system are brought forward in parallel and that a cutting edge radiobiology programme, supported by detailed cell-level simulation of the impact of ionizing radiation on tissue, is executed.

Economic impact

It is our ambition to position the members of the consortium, alone or in collaboration, to bid to deliver the ambitious R&D programme required to establish a full biomedical accelerator facility and/or to provide components or systems for such a facility. Therefore from the outset, appropriate contacts have been made with industry. Through these contacts, existing capabilities will be assessed and development needs will be quantified and documented. Each member of the consortium will thereby be positioned to take significant responsibilities in the future realisation of laser-hybrid accelerator systems and the associated R&D.

People and skills

The creation of a project team that has the diverse skill set and motivation to take the project forward to deliver the long-term goal is a clear priority. Furthermore, the sustainable development of the programme, from proof of concept to spin-out, will require staff with a breadth of experience across the disciplines. In the longer term it is our ambition to implement a staff-development programme in which early career researchers, and more established staff, recruited into one of the partner organisations will be seconded for significant periods to other members of the collaboration. To achieve our ambition it is essential to deliver a vibrant education, training and hands-on R&D programme.

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 $\sim 15\,\text{MeV}$. 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 $\lesssim 125\,\text{MeV}$. Ion beams (including C^{6+}) with energies up to $\sim 30\,\text{MeV}$ 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 1.2×10^7 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 4×10^8 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^{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.

References

[1] L. Pommarel *et al.*, "Spectral and spatial shaping of a laser-produced ion beam for radiation-biology experiments," *Physical Review Accelerators and Beams* **20** no. 3, (2017) 1–10.

[2] **The international Biophysics Collaboration** Collaboration, "Biophysics Collaboration." https://www.gsi.de/en/work/research/biophysics/biophysics_collaboration.htm, 2019.

[3] **CCAP** Collaboration, "Centre for Clinical Application of Particles." https://www.imperial.ac.uk/clinical-application-of-particles/.

[4] A. Kurup *et al.*, "Simulation of a Radiobiology Facility for the Centre for the Clinical Application of Particles,". Presented at the Third Geant4 International User Conference at the Physics-Medicine-Biology frontier, 29–31 October 2018, Bordeaux, France.

[5] C. Hunt *et al.*, "Design of LhARA - Laser Hybrid Accelerator for Radiobiological Applications,". Presented at the 10^{th} International Particle Accelerator Conference (IPAC'19), Melbourne, Australia, May 2019, paper THPGW001.

[6] R. Atun *et al.*, "Expanding global access to radiotherapy," *The Lancet Oncology* **16** no. 10, (2015) 1153–1186.

[7] A. Lühr *et al.*, "Radiobiology of Proton Therapy: Results of an international expert workshop," *Radiotherapy and Oncology* **128** no. 1, (Jul, 2018) 56–67.

[8] R. Carter *et al.*, "Complex DNA Damage Induced by High Linear Energy Transfer Alpha-Particles and Protons Triggers a Specific Cellular DNA Damage Response," *International Journal of Radiation Oncology*Biology*Physics* **100** no. 3, (Mar, 2018) 776–784.

[9] R. Carter *et al.*, "Characterisation of Deubiquitylating Enzymes in the Cellular Response to High-LET Ionizing Radiation and Complex DNA Damage," *International Journal of Radiation Oncology Biology Physics* (2019) .

[10] **PTCOG** Collaboration, "The Proton Therapy Co-Operative Group." https://www.ptcog.ch.

[11] M.-C. Vozenin, J. Hendry, and C. Limoli, "Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken," *Clinical Oncology* **31** no. 7, (Jul, 2019) 407–415.

[12] M. Durante, E. Brauer-Krisch, and M. Hill, "Faster and safer? FLASH ultra-high dose rate in radiotherapy," *The British Journal of Radiology* **91** no. 1082, (Nov, 2017) 20170628.

[13] F. Meot *et al.*, "The FFAG & and medical application project RACCAM," *Conf. Proc.* **C060626** (2006) 2308–2309. [,2308(2006)].

[14] F. Meot, "The RACCAM FFAG project," *AIP Conf. Proc.* **981** no. 1, (2008) 351–353.

[15] D. Neuvglise and F. Mot, "An Alternative Design for the RACCAM Magnet with Distributed Conductors," in *Particle accelerator. Proceedings, 23rd Conference, PAC'09, Vancouver, Canada, May 4-8, 2009*, p. FR5REP095. 2010. http://accelconf.web.cern.ch/AccelConf/PAC2009/papers/fr5rep095.pdf.

[16] K. Peach *et al.*, "PAMELA - A Model for an FFAG based Hadron Therapy Machine," *Conf. Proc.* **C070625** (2007) 2880. [,2880(2007)].

[17] K. Peach, "Accelerators for charged particle therapy," *Int. J. Mod. Phys.* **A29** no. 14, (2014) 1441001.

[18] G. Haugeberg and S. Kriz, "Tilleggslidelser blant psykisk utviklingshemmede.," *Tidsskrift for den Norske laegeforening* **110** no. 13, (1990) 1655–1659. arXiv:1405.2657.

[19] W. Luo, E. Fourkal, J. Li, and C. M. Ma, "Particle selection and beam collimation system for laser-accelerated proton beam therapy," *Medical Physics* **32** no. 3, (2005) 794–806.

[20] B. Hegelich *et al.*, "Laser acceleration of quasi-monoenergetic MeV ion beams," *Nature* **439** no. 7075, (2006) 441–444. arXiv:0612175 [physics].

[21] H. Schwoerer *et al.*, "Laser-plasma acceleration of quasi-monoenergetic protons from microstructured targets," *Nature* **439** no. 7075, (2006) 445–448.

[22] U. Linz and J. Alonso, "What will it take for laser driven proton accelerators to be applied to tumor therapy?," *Physical Review Special Topics - Accelerators and Beams* **10** no. 9, (2007) 1–8.

[23] S. D. Kraft *et al.*, "Dose-dependent biological damage of tumour cells by laser-accelerated proton beams," *New Journal of Physics* **12** (2010) . arXiv:15334406.

[24] S. Auer *et al.*, "Survival of tumor cells after proton irradiation with ultra-high dose rates," *Radiation Oncology* **6** no. 1, (2011) 139. http://www.ro-journal.com/content/6/1/139.

[25] C. Palmer *et al.*, "Monoenergetic proton beams accelerated by a radiation pressure driven shock," *Physical Review Letters* **106** no. 1, (2011) 1–4. arXiv:1006.3163.

[26] A. Yogo *et al.*, "Measurement of relative biological effectiveness of protons in human cancer cells using a laser-driven quasimonoenergetic proton beamline," *Applied Physics Letters* **98** no. 5, (2011) 18–21.

[27] D. Doria *et al.*, "Biological effectiveness on live cells of laser driven protons at dose rates exceeding 109Gy/s," *AIP Advances* **2** no. 1, (2012) 0–6.

[28] K. Zeil *et al.*, "Dose-controlled irradiation of cancer cells with laser-accelerated proton pulses," *Applied Physics B: Lasers and Optics* **110** no. 4, (2013) 437–444.

[29] S. Busold *et al.*, "Shaping laser accelerated ions for future applications - The LIGHT collaboration," *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* **740** (2014) 94–98.

[30] U. Masood *et al.*, "A compact solution for ion beam therapy with laser accelerated protons," *Applied Physics B: Lasers and Optics* **117** no. 1, (2014) 41–52.

[31] O. Zlobinskaya *et al.*, "The Effects of Ultra-High Dose Rate Proton Irradiation on Growth Delay in the Treatment of Human Tumor Xenografts in Nude Mice," *Radiation Research* **181** no. 2, (2014) 177–183. http://www.bioone.org/doi/10.1667/RR13464.1.

[32] D. Higginson *et al.*, "A novel platform to study magnetized high-velocity collisionless shocks," *High Energy Density Physics* **17** (2015) 190–197.

[33] U. Linz and J. Alonso, "Laser-driven ion accelerators for tumor therapy revisited," *Physical Review Accelerators and Beams* **19** no. 12, (2016) 1–8.

[34] F. Wagner *et al.*, "Maximum Proton Energy above 85 MeV from the Relativistic Interaction of Laser Pulses with Micrometer Thick CH2 Targets," *Physical Review Letters* **116** no. 20, (2016) 1–5.

[35] U. Masood *et al.*, "A light-weight compact proton gantry design with a novel dose delivery system for broad-energetic laser-accelerated beams," *Physics in Medicine and Biology* **62** no. 13, (2017) 5531–5555.

[36] **A-SAIL** Collaboration, "Advanced Strategies for Accelerating Ions with Lasers." http://www.qub.ac.uk/research-centres/A-SAILProject/.

Data Management Plan

This data management plan covers all aspects of any data taken during this project, including raw data, processed data, meta data, their curation, distribution and dissemination. It also covers data processing and software developed within the project. This project is fully committed to Open Data and will follow the principles as described in the Concordat on Open Research Data[1] developed by the UK multi-stakeholder group. In this way we will ensure that the data generated by the project can be a useful to the community at large.

Radiobiological Data

As there are no ethical issues concerning radiobiological data, all such data generated in this project will be made publically available in full in their most useful form. This will include all appropriate meta data needed that is needed to analyse the data. This project will build a prototype open repository for radiobiological data from this project allowing all members of the project team ***and others*** to access it.

Creation of a repository for radiobiological data

Currently there is no general repository for radiobiological data that is similar to the HEPDATA[2] database for particle physics. Within the community there is a perceived need for such a repository. This project will set up a prototype of such a repository and use it to make the data taken in the project accessible to others. We will also offer this service to other radiobiological collaborations, possibly as part of our contribution to the International Biophysics Collaboration.

Software

All software developed by this project will be made open source and will be advertised from the data repository

Clinical Data

If this project produces any clinical data, they will be handled in accordance to NHS guidelines.

1 https://www.ukri.org/files/legacy/documents/concordatonopenresearchdata-pdf/
2 https://www.ippp.dur.ac.uk/Research/Projects/HEPDATA.html