STFC Opportunities Call - ST/T002638/1: Responses to questions from the introducers

1. Please clarify the status of the work already underway at CCAP on the LhARA CDR, and what is required to bring it to completion.

The status of the design for LhARA is summarised in the article recently published in the proceedings of IPAC'19 [1] which describes the layout and principal parameters of the Stage I accelerator system. A laser facility that may be considered a prototype of that required for LhARA is in routine operation in the Blackett Laboratory at Imperial College London. This facility is used to study particle production using a target that can be developed to meet the requirements of LhARA. A prototype of the strong focusing plasma (Gabor) lens proposed for the proton- and ion-capture system has been constructed and is being commissioned at Imperial. The beam optics required to transform the highly-divergent flux produced at the source into a monochromatic 15 MeV proton beam, uniform over the *in-vitro* biological sample is established. A vertical 90° bend is included to provide optimal conditions for the radiobiology programme. Several options for the vertical bend are being considered. In the baseline configuration the bend consists of four lattice cells based on the fixed-field accelerator (FFA) principle, exploiting either spiral-type or sector-type magnets. A similar magnet design is being considered for the system demonstrator proposed as part of the ISIS upgrade programme. Close coordination between the LhARA and the ISIS Upgrade project teams will allow the magnets required for the 90° vertical bend also to serve as prototypes for the ISIS II demonstrator.

The full end-to-end simulation of the Stage I *in-vitro* system taking into account all operational modes, including the use of the RF 're-bunching' cavities to control the bunch length, has still to be completed. The rapid acceleration required for LhARA Stage II, that is to be provided by an FFA of the type under consideration for the ISIS upgrade, has yet to be included in the simulation. The simulation of Stage II requires the completion of the design of the FFA ring, the transfer line from the Stage I system, and the transfer line to the *in-vivo* end-station.

The project team anticipates that the preparation of the end-to-end simulation of Stage I will be underway by the end of September 2019. In collaboration with ISIS personnel the initial specification of the FFA will also have been completed. Therefore, to complete the outline CDR for LhARA will require the completion of the end-to-end simulation, including acceleration in Stage II. This programme will constitute the majority of the work in the first six months and will culminate in the submission for publication of the outline CDR.

2. Please also clarify the work required to upgrade the CCC beam line to facilitate FLASH.

In a recent publication [2], evidence has been summarised from a number of studies demonstrating significant normal-tissue sparing when radiation dose is delivered at ultra-high (FLASH) dose rates ($\gtrsim 100$ Gy/s) compared with the same dose delivered at dose rates typical of present treatment regimes (5 Gy/min–10 Gy/min). However only a few of these studies have investigated the impact of FLASH protons. A beam line in the Clatterbridge cyclotron not used for treatment is available and can, in principle, deliver proton-dose rates up to 500 Gy/s. To bring this beam line into operation requires reliable and accurate dosimetry for doses of between 2 Gy and 10 Gy at dose rates up to those required to perform cellular irradiations in the FLASH regime.

The dosimetry will be carried out in collaboration with the project partners and Clatterbridge cyclotron staff (particularly Dr. Andrzej Kacperek, the Head of the Eye Proton Therapy Centre at Clatterbridge). Ion chambers and other novel fast responsive dosimeters will be provided by the CCC or one of the project partners. A simulation of the beam line has been developed by one of the project partners (CI/Liverpool) using the BDSIM package developed by CCAP personnel (JAI/RHUL). Further collaboration will be developed with the project partners and the National Physical Laboratory.

The work supported by this proposal will establish accurate dosimetry, paving the way for preliminary experiments comparing FLASH dose rates with those normally used for proton irradiations to be performed on cultured cells (e.g. cell survival and DNA damage induction) using biological end-points. The legacy will therefore be

an invaluable facility at which CCAP and LhARA personnel can deploy and test the advanced diagnostics and automated, robotic systems required for LhARA and at which they can gain expertise in radiobiological experimentation.

3. The project covers 24 months, while funding is requested for two PDRAs for 6 months each. Please clarify the project plan ; what work the PDRAs will do, and when, and what work is required by other researchers.

The resource-intensive aspects of the project are the completion of the outline CDR and the dosimetry of the beam line at the CCC. The development of the LhARA programme requires the completion of the outline CDR. This document will be used to define the key design, simulation, and prototyping activities that are required to take the programme forward. The publication of the outline CDR will be of great value in securing future funding. By providing a FLASH-enabled proton-beam facility at the CCC we shall create an important scientific and technology-development test-bed.

To take the LhARA programme forward requires that we prioritise investment in these critical elements over the first six months. Therefore, the LhARA-project priorities are well matched to the STFC requirement that applicants "*. . . are able to start on the 1 October and commit the majority of the requested resource within the period 1 October 2019 and 31 March 2020*". As explained in our proposal, we will redirect existing PDRA effort to complete the outline CDR and the CCC beam-line upgrade in the first six-months of the project.

Together, the two early-career researchers dedicated full time to the development of LhARA will leverage the effort of experienced personnel from the participating institutes to deliver the outline CDR for LhARA. During the preparation of the CDR we shall engage with stakeholders from the clinical, radiobiological, academic, and industrial communities to bring forward the proposals required to deliver the next steps in the programme. The two PDRAs employed on this award for six months will be retained, supported on resources secured within the collaborating institutes or through further competitive awards, to take forward the LhARA development programme and the scientific and technology-development programme at the CCC.

The collaboration building and networking activities required to exploit the opportunity presented by the recent formation of the International Biophysics Collaboration (IBC) will take place over the full two-year period of the award. This aspect of the programme will culminate in a strong contribution to the second IBC meeting that will take place in two years time. The LhARA project team, the CCAP, and the project partners will all be engaged in the development of the UK collaboration and the UK components of the emerging IBC programme.

4. Clarify the value added by this proposal to the overall LhARA project.

Significant progress has been made over the past year to produce a consistent and detailed parameter list for Stage I of LhARA. A concerted effort is now required to bring the specification of the full LhARA system to the same state of development, to carry out a full end-to-end simulation of the *in-vitro* and *in-vivo* systems, and to deliver a convincing outline CDR. The principal tasks that will be accomplished using the funding requested here are: an end-to-end simulation of beam transport including space-charge effects (crucial for the energy selection); a careful investigation of the re-bunching cavities to enable a large variation of dose rate; the detailing of the vacuum system and beam-line diagnostics; the production of a first engineering model of the dipoles; and the detailing of the biological end-stations.

The results will be presented, together with a detailed layout including initial considerations of infrastructure (power, cooling) and a preliminary cost estimate in the outline CDR. This work can only be performed in the given timescale if funding for the PDRAs is available. The CDR will provide the basis for further grant applications to, for example, CRUK, the MRC, EPSRC and STFC to fund the future development of the programme. Therefore the funding request to STFC is an essential step in the LhARA project. The funding will be invaluable to strengthen the national and international collaborations that have already been established with, for example, MedAustron, the Medical University of Vienna, and the Clatterbridge Cancer Centre, and enable the early start of a FLASH measurement programme before beam is available at LhARA.

References

[1] 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.

[2] M.-C. Vozenin, J. Hendry, and C. Limoli, "Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken," *Clinical Oncology* **31** (jul, 2019) 407–415.