

Response to Reviewers of Manuscript ID 567738

LhARA: The Laser-hybrid Accelerator for Radiobiological Applications

The authors would like to thank the reviewers for the insightful, constructive comments. In the preparation of this response the Reviewers' comments have been numbered as indicated in the annotated copies of the Reviewers' evaluations and supporting files appended to this response.

Additional points to put in intro para:

- Make reference in paper and response that further details on the LhARA design are contained in the pre-CDR. Include the citation!
- ...

Reviewer 1

Evaluation

1. **The major limitation is a dichotomy between excessive simplicity and verbosity in describing well-known concept (e.g. RBE) on one side and an excessive detail on technicalities regarding the design of the beam line.**

Section 2 has been redrafted to address the comments made by both reviewers relating to the style and contents of the "Motivation". We respond below to the comments from the reviewers on the level of detail in the technical description of LhARA. The principle subject of the paper is the documentation of the scientific justification of the feasibility of the development of the technologies required to deliver the novel laser-hybrid accelerator system. As described below, the authors believe that the present level of description of the laser-driven source, the novel capture system, and novel accelerator system is required for a scholarly work and for the results presented to be verified independently.

2. **...there appears to be a vagueness about the actual implementation of such an ambitious and clearly extremely well-thought out programme: no time frame, no cost-effectiveness evaluation, no mention on the actual overall cost.**

The paper was written to document the concepts and technologies that underpin the novel laser-hybrid accelerator concept. The consortium has prepared a "pre-CDR" document which contains an initial evaluation of both the cost and the schedule. Our analysis indicates that, assuming sufficient resource, LhARA stage 1 could be executed over a 5-year period.

The pre-CDR is cited in the paper. The authors believe that it is not appropriate to publish either the cost nor the schedule for the facility. Such information is sensitive and is subject to revision in the light of funding pressures and competing priorities among the funders, consortium, and other stakeholders.

3. **Although I checked that the reference list is adequate, there is a disagreement on two of those, which I strongly believe must be replaced as illustrated in the attached detailed report.**

The authors thank the reviewer for the comment and have revised the bibliography accordingly.

Review supporting file – 48618

1. **On the other hand, it seems extremely simplistic in some basic aspects particle radiobiology as is the case for the explanation of the difference of biological effectiveness and DNA damage between photons and high-LET particles.**

As noted under point 1 above, the authors agree with both reviewers in regard to the style and content of the introductory sections of the paper. Section 2 has been redrafted and compacted in the light of the comments of both reviewers.

- 2. I understand that this information was used in simulations, but is such a degree of detail necessary? The essential table is arguably the last one, Table 5, where the true relevant information for radiobiological experiments is reported, i.e. the dose per pulse, as the instantaneous and average dose rates achievable with the two types of particles chosen for the simulation, the low- and high-energy protons and C ions.**

The authors believe that the information provided in the text and the various tables is essential to justify the performance of the facility presented in figures 5, 8, 10, and 11 and in table 5. The novel combination of a laser-driven source, with a strong-focusing plasma lens, and fixed-field alternating-gradient acceleration has enormous potential but its performance has not been demonstrated. Therefore, it is important that the reader be provided with details sufficient for the claimed performance of the facility to be validated.

- 3. ... what is the time scale of the project? Can the authors say a date by which stage 1 and/or stage 2 will be initiated/completed? What is actually the funding status? It is understood this is part of a well-structured Consortium but has LhARA, as described, been already granted funding for its complete implementation? Also, only towards the very end of the manuscript (line 758) the reader learns that “It is envisaged that LhARA will be built at an STFC National Laboratory or equivalent research institute which has an established safety-management system and culture in place”. So, hasn’t even the building site been decided yet? This may also help to corroborate a rather important statement at line 273 “ At present, a dedicated ion beam for radiobiology, based on a laser-driven source, is not available anywhere in the world. Therefore, LhARA will be a unique, state-of-the-art system, able to explore the radiobiological benefits of a laser-accelerated ion source”. Yes, true, that depends on the time scale and the implementation feasibility.**

Resources to allow the present concept for LhARA to be developed have been provided by the UK Science and Technology Facilities Council (STFC) and by members of the consortium. The consortium is now actively engaged with the STFC, other UK funding agencies, and stakeholders with the goal of securing the resources necessary to take the programme forward. The focus at the moment is on delivering the R&D required to demonstrate that the principal technical risks (the laser-driven target, plasma-lens capture system, and the instrumentation and dosimetry) are properly under control.

The site for the facility has not been decided. Discussion of the possibility that the LhARA initiative could be developed by the consortium in collaboration with the STFC Laboratories have been initiated. In the UK, the Daresbury or Rutherford Appleton Laboratories seem to offer the most natural potential sites for the eventual implementation of LhARA.

The foci of the present paper is on the LhARA concept, the underlying science, and the technical feasibility of the various systems that will be required. The authors are aware of the importance of the issues raised by the reviewer and are active in trying to address each of them. However, we do not believe it to be appropriate to include discussion of such political issues in the body of the text.

- 4. “The research project is time limited such that, should it not prove possible to produce a suitable Gabor lens, there will remain time sufficient to procure conventional solenoids in their place”. Well, then one may wonder: a) what about all the work presented after this line, based on the use of Gabor lenses, completely useless? For instance, all the work described in lines 419-426, and**

the whole design, really seems heavily Gabor lens-dependent; b) if there is really an alternative in conventional solenoids, why propose Gabor lenses in the first place? Or is there something I cannot grasp?

The authors thank the reviewer for the question and agree that the discussion of the use of a solenoid as an alternative to the Gabor lens was not clear in the original draft of the paper.

The reviewer is correct; the solenoids are an option that is being considered to mitigate the risk that the Gabor lens is demonstrated not to deliver the performance required for LhARA. The discussion of the alternative option has been revised to make it clear that the use of solenoids has been considered to demonstrate that the LhARA project is viable even in the event that the Gabor lens solution fails to meet specification.

5. **...facilities such as LhARA, or at least based on the hybrid acceleration system proposed for LhARA, will help in the direction of making PBT accessible also to those vast part of the world population that are now excluded. Am I right in understanding this statement in this sense? If so, it should be probably better argued exactly how: the whole design for LhARA does not come cheap and does require R&D investments that do not look trivial to me. Or are the authors saying that LhARA could serve as a prototype for similar facility for delivering PBT?**

The authors thank the reviewer for the observation. Indeed, the consortium continues to work to articulate both concisely and with precision its vision for the the route to reducing the cost and complexity of a clinical system using the laser-hybrid technique. The consortium believes that it is the combination of the triggerable, laser-hybrid acceleration coupled with a sophisticated fast feedback and control system that incorporates real-time dose-deposition imaging that has the potential to reduce the need for a large gantry, thereby making the whole clinical system more compact. The authors have revised the relevant statements to make the case more clearly.

6. **...nowhere it is cited for instance that hypothesis such as the oxygen depletion or other radiochemical phenomena will be investigated with an array of energies and ion species which will be truly unique ...**

We appreciate the reviewer for their comment and obviously agree that oxygen depletion and the ability to investigate a range of energies and species is a unique capability of the proposed facility. This has now been further stressed into the Motivation section.

7. **I am specifically referring to the sentence at line 205 “In addition, LhARA will enable exhaustive evaluations of RBE using more complex end-points (e.g. angiogenesis and inflammation) in addition to routine survival measurements”, and this concept is repeated elsewhere as well.**

It's unclear what the reviewer is referring to here, however our intention was to highlight the broad range of radiobiological end-points that could be measured with LhARA, that are not possible at other clinical facilities due to the lack of appropriate laboratory and associated equipment. This point has been repeated on only one other occasion with the document, in the relevant Biological End-Station section.

8. **There is indeed a tendency on repeating over and over the same concept, i.e. that LhARA is going to be a novel facility allowing unprecedented research, and sometimes the same exact sentence. For example, “The laser-driven source allows protons and ions to be captured at energies significantly above those that pertain in conventional facilities, thus evading the current space-charge limit on the instantaneous dose rate that can be delivered” in the Abstract (line 10 and subsequent), in the Introduction (lines 72 and subsequent) and later on line 227, page 13. The same repetition occurs**

for the concepts of the exciting finding related to FLASH and micro-beams from line 63 and from line 193.

The authors appreciate the reviewer's comment and have removed inappropriate repetition from the manuscript.

9. **Reducing the length of the manuscript (28 pages without references), considering the above-mentioned unbalance, should be corrected maybe moving part of the more technical information to an appendix or supplemental material.**

The length manuscript has been reduced by removing the more "basic" material from section 2 and revising section 1. The paper documents the authors' study of a novel, perhaps paradigm-changing, technique for the delivery of proton and ion beams for biomedical applications. In contrast to other comparable proposals, the authors seek to exploit the plateau region in the laser-driven proton and ion spectrum to provide a beam that is stable shot to shot. Acceleration to high energy is provided by means of a novel fixed-field alternating-gradient accelerator (FFA) that has the advantage that the rapid acceleration is flexible and can accelerate protons and ions from helium to carbon. The authors therefore feel that the technical detail is necessary both to justify the performance quoted in section 4 and to provide a scholarly work that allows the findings to be validated by an interested reader.

10. **Paragraph 2 Motivation is unnecessarily long.**

The authors have accepted this comment which was made by both referees and the text has been revised accordingly.

11. **Line 117: maybe adding a reference?**

This statement has been removed in cutting down this section, so a reference is no longer required.

12. **Line 153: Is this statement really necessary, concerning the observed increase of RBE at distal position along proton SOBPs "Some of this variation may be due to the positioning of the cells during irradiation relative to the Bragg peak". Here the authors are broadly illustrating theoretical basis for uncertainties affecting particle radiobiology; implying that some published results may be due to banal positioning errors, that may be true, but it reads out of context here.**

We agree with the reviewers comment and nevertheless in revising the Motivation section, this statement has now been removed.

13. **From line 156: as said before, most concepts can be summarized and also poised in a slightly more rigorous manner. RT does not just induced cell death by DNA damage, there is Therapy-Induced Senescence (TIS) affecting cancer cells' microenvironment with its related Senescence-Associated Secretory Phenotype (SASP), but it's just an example.**

We hope that the revised Motivation section now addresses this point also, where the concepts are summarised in an appropriate manner.

14. **Line 184: apart from being a repetition of what already said in the introduction, the sentence saying that RT is administered in daily fractions of 2 Gy, here it is said at dose rates of 5 Gy/min or less, in the Intro of 10 Gy/min less. If this sentence really must be repeated, may it be done so consistently?**

This statement has now been removed from this section.

15. **Lines 190 and subsequent, on the dose rate at which the FLASH effect is observed: I would strongly suggest the authors to change the references Systems (200) and IBA (2019). One actually points to a press release concerning the first patient treated with FLASH-RT. Please use a scientific paper, which was published exactly on that: Bourhis J, Sozzi WJ, Jorge PG, Gaide O, Bailat C, Duclos F, Patin D, Ozsahin M, Bochud F, Germond JF, Moeckli R, Vozenin MC. *Radiother Oncol.* 2019 Oct;139:18-22. doi: 10.1016/j.radonc.2019.06.019. Epub 2019 Jul 11.**

We appreciate the reviewers suggestion, and have now added the requested reference relating to the first patient treated with FLASH RT, albeit using electrons.

16. **From line 306 to 312 it reads as a repetition of a concept said abundantly before.**

The authors accept the reviewer's comment and have removed the paragraph.

17. **Caption of Fig.3: has really the figure relative to the length of the beam line to be given with this accuracy, 17.225 m?**

The authors accept the reviewer's comment and have reduced the precision with which the length of the beam line is reported.

18. **Line 474: is the aberration issue observed in the simulations as in fig. 4 going to be solved/mitigated by using Gabor lenses? Because that is what seems to me the authors are stating when saying they will replace the solenoids used with a full electromagnetic simulation of these lenses. Again, what if the use of Gabor lenses will be not feasible? Is a risk mitigation plan in place?**

The aberration referred (shown in figure 5) is indeed a concern as it demonstrates that the optics is not linear. This effect is currently being investigated. Despite the non-linearity observed in the simulations, the lattice presented in the paper is able to deliver a uniform dose distribution at the end station. It is expected that the Gabor-lens focusing will behave in a similar way. However, the focusing of off-momentum particles in the Gabor lens will differ from that of the equivalent solenoid. This will change the form of the aberrations to some extent. The current results show that we can achieve the beam quality required if it becomes necessary to use the equivalent solenoids.

The authors hope that these comments clarify the situation. We propose not to alter the text as we feel it describes accurately the properties of the beam delivered to the end station.

19. **Fig. 6: Are the numbers on both y-axes intended to be followed by a full stop, i.e. 50. 100. and -3. -2. and so forth?**

The decimal points indicate that the values on the axes are not integers. The figure will be revised in line with the journal's editorial practice at proof stage.

20. **Line 722: the sentence "will enable multiple groups of researchers to perform productive and high-quality biological research" referred to the state-of the-art lab..well, isnt' high-quality, productive research what we all strive to do? That is helped by having a good, fully equipped lab. I would omit that, please, it sounds appropriate in a Grant application, probably not here.**

The authors accept the reviewer's comment. This sentence has been deleted.

21. **Line 757: the acronym STFC suddenly appears. It should be explicated, not all readers will be from the UK.**

The authors accept the reviewer's comment. Reference to STFC has been removed.

22. **Line 787: the 30-micron cell thickness was of course need to put a number to use in the simulations but I am confident the authors know that unless each single time they place a monoayer under the beam, they will not expect its thickness to be measured, right? And generally single monolayers are a bit thinner than that in normal cell culture conditions.**

The authors accept the reviewer's comment. The dimensions were introduced to define the configuration used to simulate the dose delivered to the end stations. In operation the experimenters will need to assess the degree of variation in the thicknesses of the various materials in the path of the beam. The development of the techniques necessary to ensure that the dose deposited in the cell layer is accurate will be the focus of work in the R&D phase.

23. **Line 793: when depth is mentioned depending on the energy, actually is a SOBP achievable or the LhARA beams will have pristine Bragg peaks? Maybe this information could be provided/clarified/mentioned? It may not so obvious to the reader.**

It is possible to deliver a SOBP at LhARA, indeed our goal is to be able vary the beam energy within one bunch. Two cavities are provided for this purpose in the stage 1 beamline. In stage 2 the flexibility to manipulate the longitudinal phase space provided by the RF in the FFA is augmented by the 5-cavity module placed in the *in vivo* beam line. A statement to this effect has been added in the text.

24. **Lines 855-856 "tumour control probability" sound more appropriate than tumour-kill probability"**

The sentence has been modified to refer to "tumour-control probability".

Reviewer 2

Evaluation

1. **There are not "main finding": the paper is more a technical report on a facility planned to be realised. English is perfect and reported information are oversized as respect a scientific paper**

The paper documents the authors' study of a novel, perhaps paradigm-changing, technique for the delivery of proton and ion beams for biomedical application. The proposed configuration is unique as it combines the use of a short-pulse laser to create a large flux of protons or ions that are captured efficiently by a combination of novel, strong-focusing plasma lenses. In contrast to other comparable proposals, the authors seek to exploit the plateau region in the laser-driven proton and ion spectrum to provide a beam that is stable shot to shot. Acceleration to high energy is provided by means of a novel fixed-field alternating-gradient accelerator (FFA) that has the advantage that the rapid acceleration is flexible and can accelerate protons and ions from helium to carbon.

The main findings of the study are that it has been possible to devise a self-consistent design that exploits at once the key features of the laser-driven source, the strong-focusing plasma lens, and the FFA to deliver a uniquely flexible source for radiobiology using technologies that have the potential to be developed to drive a step change in clinical capability.

2. **The paper report the status of development of the LhARA project. It appears as a technical report more than a scientific paper so the strong recommendation s to change the format, removing unuseful technician section while going directly inside the scientific points.**

The paper documents the design for a novel acceleration system that has the potential to drive a step-change in the exploitation of proton and light-ion beams. The authors feel that only the technical detail necessary to justify the claims made in the paper is given. The level of detail has been determined by the need to provide a scholarly document and to provide the interested reader with detail sufficient for

the performance of the facility at both stage 1 and stage 2 to be verified. In considering the referee's comment we have reviewed the contributions to the literature on novel accelerator technologies (see for example [1–7]) and feel that the level of detail provided is appropriate.

3. **Are the methods sufficiently documented to allow replication studies? “No”.**

The authors believe that the detailed description of the laser-driven source, the novel plasma lens, and the accelerator facility provided in Section 3, in combination with the bibliography, contains sufficient information for the studies presented in the paper to be replicated and the claims of the paper to be verified.

Review supporting file – 47477

1. **The work, indeed, appears more a technical report other than a scientific paper. It must be reduced. The long technical sections must be deleted while authors should more rapidly concentrate on the characteristics of the final beams that will be of interest for the community.**

The authors justification of the level of the technical description of the facility has been given above. The performance of the facility at the end-stations is reported in figures 5, 8, 10, and 11 and in table 5.

Review supporting file – 48170

1. **On which basis this statement can be done?**

The reviewer's question relates to the statement “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 response of tissue to ionising radiation is governed by chemical processes that take place over time periods of up to a second. Biological response processes evolve over longer timescales (minutes to hours). As explained in the text, the laser-driven source for the LhARA beam is triggerable and the beam transport and post-acceleration is rapid. Therefore LhARA has the ability to provide radiation at arbitrary intervals timed to interrupt the evolution of both the chemical and biological pathways.

2. **Referring to Section 2: This section is almost a repetition of very basic concepts and should be reduced.**

The authors accept the reviewer's comment. Section 2 has been revised to take into account this comment and the other related comments made by both reviewers.

3. **Referring to the paragraphs following the sub-title “The case for a systematic study of the radiobiology of proton and ion beams”: Too long section. This is good for a project proposal submission not for a scientific paper. I recommend to reduce this part discussing with more details on the aspects related to the facility development.**

The authors accept the reviewer's comment. Section 2 has been revised to take into account this comment and the other related comments made by both reviewers.

4. **Referring to the comment “...thus evading the current space-charge limit ...” on line 229: Never the concept of 'space-charge limit' was explained: can you please explain it in some point before?**

The text has been revised to define the concept of space charge.

5. **Referring to the comment “...has a modest (5%) energy spread ...” on line 234: Can you please**

add at least a reference paper where the mentioned characteristics of the electron beams are experimentally demonstrated?

The authors thank the reviewer for his comment and apologise for the claim of a 5% energy spread in the electron-energy spectrum arising from the laser-target interaction. Indeed, the properties of laser-driven electron beams is not pertinent to the principle thrust of this paper. Therefore, the reference to laser-generated electron beams has been removed. The text has also been updated to take into account the recent publication of measurements of the the shot-to-shot stability of laser-generated proton beams. An appropriate citation has also been added.

6. Referring to figure 1: What the grey cylinders represent? Where are the ‘Gabor’ lens are?

The caption of figure 1 has been updated to identify the various elements of the beam lines.

7. Referring to the comment that “...LhARA will be a unique, state-of-the-art system, able to explore the radiobiological benefits of a laser-accelerated ion source” on lines 273–275: This is not true, as the ELIMED (ELI-BEAMLINES, CZ) beam line that is almost in its commissioning phase, will provide a dedicated point for such studies: please comment and ad a proper reference.

The authors thank the reviewer for this comment and apologise for the oversight. An appropriate discussion with citations has been added.

8. Referring to the comment “... the two-temperature energy spectrum of the laser-accelerated beam” on line 291: Can you please provide a plot showing this ‘two temperature’ spectrum?

The two-temperature energy spectrum is a well known feature of particle distributions generated by target normal sheath acceleration (see [8, 9]). These citations have been added to justify the statement.

9. Referring to the comment on the existence of a “...a cloud of electrons ...” on line 339: How is it produced? No explanation of the lens principle is given!

The comment refers to Gabor’s realisation that the field created by a cylindrically symmetric electron cloud could be used to focus a positive ion beam. In Gabor’s electron-plasma lens the electron cloud was created using a hot cathode. This paragraph is designed to explain the focusing principle of the lens which does not depend on how the electron cloud has been created. The authors therefore propose that the text be left unchanged.

10. Referring to lines 306–312: This is a repetition of concepts that should be avoided in a scientific paper.

The authors accept the reviewers comment and have removed the paragraph.

11. Referring to lines 313–320: Also this paragraph does not give substantial information: I propose to remove it.

The authors accept the reviewers comment and have removed the paragraph.

12. Referring to the caption to figure where the collimated of is indicated by a black vertical bar, the reviewer’s comment is that: It seems green ...

While the caption of figure 3 describes accurately the beam-line elements shown in the figure, the authors accept that the figure should be self-explanatory. A legend has been included in the figure.

13. **Referring to line 410 where the energy spread of the idealised Gaussian proton is quoted to have been 1×10^{-6} MeV, the reviewer asks: is this value realistic?**

The sentence which starts on line 409 and ends on line 410 defines the properties of the idealised beam that was used to evaluate the performance of the optics of the stage 1 beam line using a quasi-mono-energetic beam. To do this an energy spread of 1×10^{-6} MeV was chosen. Such a small energy spread can not be achieved in practice, but, is a practical means by which to simulate a mono-energetic beam. Although it has not been presented here, the beam produced by the laser-driven source has been simulated to provide a more accurate kinetic-energy spectrum. A large fraction of the particles generated were lost in the capture section of the beam line. While such losses are expected in the capture section, the result was that the statistical weight of the particles tracked along the remaining beam line was low, resulting in large statistical uncertainties in the beam parameters at the end station. Work is already underway to improve the generation of the particle flux produced at the laser-driven source. This work will continue as part of the R&D programme and will lead to further optimisation of the optics of the LhARA beam lines using these more realistic input beams.

14. **At the start of section 3.4.5 the reviewer asks: Can you explain why the same beamline cannot be used for in-vivo and in-vitro?**

In principle, both the high-energy *in vitro* and the *in vivo* beam lines can support both *in vitro* and *in vivo* experiments. The authors have separated the functions of the two end stations in order to facilitate efficient small-animal handling. The position of the *in vivo* end station has been conceived to be adjacent to the principal road access to the facility. The text has been modified to make this clear.

15. **At the start of section 3.4.4 the reviewer asks: Important information useful for the Users are missed (like the final energy, the range, if the beam exits in air and how long is the in-air section ...)**

The authors have paid particular attention to the specification of the low-energy *in vitro* end station since the low beam energy presents particular challenges in the beam transport, instrumentation, and dosimetry. Information on the air gap, energy, and range (in graphical form) for the low-energy *in vitro* end station are presented in figure 11. The detailed specification of the high energy *in vitro* and the *in vivo* end station has not yet been completed. However, the energy range and parameters of the beam at the end station are reported in Section 3. Simulations have been performed, reported in Section 4, to evaluate the dose that can be delivered. The beam parameters (energy, beam size) are presented here.

16. **Figure 11: referring to the initial peak in energy loss, the reviewer asks: What is this?**

The loss between 0 m and 0.005 m is deposited in the vacuum window and the scintillating fibre of the final beam-monitoring detector. The sketch above the figure is intended to allow the reader to infer the material through which the beam passes. The caption of figure 11 has been updated to make the connection between the energy loss observed in the figure and the material presented in the sketch.

17. **At line 801 the reviewer comments: Which detector, independent from dose-rate, are you planning to use for absolute dosimetry? Markus is not, probably, the best choice.**

The Markus detector is widely used in dosimetry of proton and hadron beams. The size of the active volume of the Markus PTW 23343 ion chamber was used in the dose calculations so that the dose rates quoted could be compared to other facilities in operation. The authors have updated the description of the calculation performed to estimate the dose rates to make this clear.

The authors are active in the discussion of the dosimetry that will be required for LhARA. Various op-

tions are under consideration and further work is required before a choice can be made.

References

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