

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.

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.**

Response.

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.**

Response.

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.**

Response.

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.**

Response.

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.**

Response.

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.

Response.

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?

Response.

5. 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?

Response.

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 ...

Response.

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.

Response.

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 microbeams from line 63 and from line 193.

Response.

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.

Response.

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

Response.

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

Response.

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.**

Response.

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.**

Response.

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?**

Response.

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.**

Response.

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

Response.

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?**

Response.

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?**

Response.

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?**

Response.

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.**

Response.

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

Response.

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.**

Response.

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.**

Response.

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

Response.

Reviewer 2

Evaluation

1. **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 pointsComment.**

Response.

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

Response.

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.**

Response.

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."

Response.

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

Response.

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.

Response.

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?

Response.

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?

Response.

6. 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 add a proper reference.

Response.

7. 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?

Response.

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

Response.

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

Response.

10. **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!**
Response.
11. **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 ...**
Response.
12. **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?**
Response.
13. **Referring to section 3.4.4 the reviewer comments: Important information useful for the Users are missed (like the final energy, range, if the beam exits in air and how long is the in-air section ...)**
Response.
14. **At the start of section 3.4.5 the reviewer asks: Can you explain why the same beeline cannot used for in-vivo and in-vitro?**
Response.
15. **Figure 11: referring to the initial peak in energy loss, the reviewer asks: What is this?**
Response.
16. **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.**
Response.