

**Title: LhARA: The Laser-hybrid Accelerator for
Radiobiological Applications**

General comments

This paper describes the conceptual and technical design of a novel particle accelerating facility, LhARA, which by assembling an innovative combination of high intensity-powered laser-driven generation and plasma lenses-assisted focussing of ions with fixed-field alternating-gradient accelerator (FFA), promises to deliver a uniquely flexible research environment for carrying out basic research in the radiobiology of charged particles. The ultimate objective is to allow faster proton and ion-beam therapy (PBT), which should be also better biology-based, hence suitably targeting the individual patient characteristics, thanks to the new insights that the peculiar and so far unattained physical features on the spatio-temporal structure of mechanisms through which ionizing radiation (IR) interacts with the biological matter. The authors state that the system envisaged by the LhARA system, will allow unprecedented flexibility in terms of switching between ion type and energies, which in turn should lead to the possibility of exploring the therapeutically beneficial promises (and the radiobiological mechanisms at play thereof) held by the recently discovered FLASH effect and by the micro-beam approach, both pointing toward in the direction of reducing normal tissue radio-toxicity. It is also hinted at the fact that by making PBT delivering facilities more compact, such a form of treatment will be made more readily accessible to a wider cancer patient audience, with obvious societal consequences.

LhARA, as presented by the authors in this paper, arguably implies a huge technological effort and tremendous potential for scientific breakthroughs and fits within the scope of the Research Topic “Applied Nuclear Physics at Accelerators” that stemmed from the GSI Biophysical collaboration meeting held in 2019 aimed at creating a network of novel and existing applied physics research infrastructures.

The paper is extremely detailed and highly technical in the sections devoted to the description of the laser and plasma-based modalities, with a plethora of information. 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. ¹ This, incidentally, takes almost more than half page whereas it can be condensed in a sentence and appropriate reference. Such a dichotomy also creates an unbalance between what reads as a “lay explanation “of well-known concepts such as the long-debated RBE uncertainty for clinically used proton beams, for example, which according to the authors research performed at LhARA will contribute to solve, and instead highly specific descriptions of advanced laser acceleration and focussing techniques. At times, the reader has the impression that the original research part that is arguably present in the paper (see for instance the Monte-Carlo simulations and similar) is masked and suffocated by an engineer-like layout of the project. Details such as the length (17,225 metres) of a beamline, with tables (e.g. Table 2) that contain an amount of specifications down to the number of solenoids or the bending angle seem more useful on the workers on the constructing site than to the researcher who is interested to carry out his experiments in the new facility. 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. ²

Within the wealth of information provided, there are some points that may be of interest, and actually important in the presentation of such a massive R&D programme: 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. 3

One important innovation among the so many proposed here, it seems to me, will be the use of Gabor lenses. Of course, it is going to be exciting research to see if the criticalities that are pointed out by the authors can be overcome, i.e. the instability of the electron cloud. However, I find the statement on line 393 of a rather disarming naivety “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? 4

Conceptually, one of the motivations to think of an alternative to conventional accelerators for hadrontherapy, besides their limitations in term of time to dedicate to pre-clinical research, is, of course, cost and size, hence complexity. This has driven researchers such as those involved in this ambitious programme to strive for compactness and cost-effectiveness. Moreover, it is stated in the introduction “It is estimated that 26.9 million life-years could be saved in low- and middle-income countries if radiotherapy capacity could be scaled up [Atun et al. (2015)]. Novel techniques incorporated in facilities that are at once robust, automated, efficient, and cost-effective are required to deliver the required scale-up in provision”. This hints at the possibility that 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? 5

Still, on the conceptual side: it is stated repeatedly that LhARA will allow radiobiology research that is not possible to do now at existing facilities. However, one thing is the time scale of dose administration that will be achievable, which is indeed a “terra incognita” as correctly stated by the authors, since the mechanistical bases for such effects are not known (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), another thing is the “type” of endpoints. These are unrelated to the specifications of LhARA. There possibility of performing experiments using endpoints other than clonogenic survival, such as senescence or study of pro-inflammatory mechanisms or more sophisticated biomolecular investigations. This will be made possible by the state-of-the art radiobiology laboratory that will be annexed to the accelerating complex, and of course by the ability and expertise of the users. 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. 6

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

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.

Punctual remarks

Paragraph 2 Motivation is unnecessarily long. Some concepts are trivialized, it seems that the Lay Summary extends into this section as well. For instance, “Dose delivered to healthy tissues can cause the death of the healthy cells and create adverse side effects” makes a lay reader believe that the RT side effects stems solely by cell killing, but this paper speaks to a community that is well aware that the scenario is more complex than that.

Line 117: maybe adding a reference?

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.

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.

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?

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.](#)

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

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?

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?

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?

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.

Line 757: the acronym STFC suddenly appears. It should be explicated, not all readers will be from the UK 20

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. 21

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. 22

Lines 855-856 “tumour control probability” sound more appropriate than tumour-kill probability” 23