Final

Report from the Review Panel

Pre-publication review of the LhARA pre-CDR

Remote - hosted at Imperial College London

31 March 2020

Review website:
https://ccap.hep.ph.ic.ac.uk/trac/wiki/Research/DesignStudy/PreCDR/Review

Review Committee

Paul Bolton; Munich
Mike Lamont; CERN
Yolanda Prezado; Curie Institute, Paris
Francesco Romano; INFN

Invited
Malek Haj Tahar

Presentations

- J. Parsons(Liverpool) Radiobiological motivation (PPTX, PDF)
- A. Kurup, pre-CDR PM (ICL) LhARA pre-CDR overview (PPTX, PDF)
- O. Ettlinger (ICL) Laser driven proton and ion source (PDF)
- C. Whyte (Strathclyde) Proton and ion capture (PDF)
- J. Pasternak (ICL) Design of the LhARA accelerator facility (PDF)
- W. Shields (RHUL) Simulation of LhARA (PDF)
- J. Matheson (STFC RAL, PPD) Instrumentation (PPTX, PDF)
- J. Hughes (Liverpool) Biological end stations (PPTX, PDF)
- G. Aymar (STFC RAL, ISIS) Infrastructure considerations (PPTX, PDF)

Summary

LhARA is clearly an interesting and well motivated proposal. The potential of the facility to provide ground breaking capabilities to the radiobiological community were clearly stated and supported by representatives of the interested parties. From an accelerator physics perspective, the novel proposal offers a number of clearly recognized challenges. There is high potential with some unique features; the flexibility and beam characteristics offered by the facility is attractive.

On the accelerator front, there appears to be a clear R&D roadmap to address the technical challenges. None appear, at this stage, to be insurmountable and the panel is confident that, given sufficient resources, these challenges can be met. In doing so, the field will potentially help develop methods and technological solutions with a wide range of applications.

Given that the proposal is in the pre-CDR phase, the team is to be congratulated for the impressive progress made so far.

Recommendations

We recognize that the project is at the pre-CDR stage and clearly there are a number of open issues that are recognized and will be addressed in due course.
Higher level recommendations:

- Consider beam requirements of ultra-high dose rates and high doses per pulse to explore a wide range of temporal regimes and achieve the doses necessary for facilitating full investigation of the FLASH effect.
- Fully develop variable energy aspects of the FFA in the CDR phase and address potential risks therein.
- A wide variety of domains are implicated (Laser sources, plasma, Gabor lens, specialized magnets, RF, beam transfer, accelerator physics, beam instrumentation, controls etc.). Ensure appropriate levels of resources to ensure the required developments in all these areas.

General Comments

Yolanda Prezado

LhARA, Laser-hybrid Accelerator for Radiobiological Applications, is conceived as a novel and very versatile facility devoted to charged particle radiobiology research. LhARA uses a hybrid approach in which laser-driven beams are post-accelerated by a fixed-field accelerator (FFA). This approach enables radiobiological investigations in completely new regimes as it allows the unique properties of the laser-driven source—extremely high instantaneous flux in an extremely short pulse over a tiny area, flexibility in the time and spatial structure of the beam —to be preserved and exploited.

This is a very promising project, offering unique beam features and much-needed research infrastructure for radiobiology research. The main characteristics to be highlighted are:

- **Flexibility:** The flexible temporal and spatial beam structure would enable exhaustive investigations of the impact of the beam parameters (i.e. pulse length, repetition rate, average dose rate) on the biological response. These comprehensive evaluations are not possible at clinical centres, where the clinical beams cannot be tuned. Among others, this flexibility would allow assessing the precise beam characteristics required and the thresholds in Flash therapy. Along this line, LhARA may also contribute to unravel the underlying mechanisms in Flash therapy.
- **Different beam species:** The availability of several ion beams (from protons to heavier ions) at the same facility will aid the inter-comparisons among different charged articles for therapy.
- **Accessibility:** The greater accessibility of LhARA in comparison to clinical centres would allow:
- The assessment of different temporal fractionation schemes. Linked to that, evaluations of different combinations with immunotherapy or chemotherapy could be performed with fewer constraints than at clinical centres.
- performing exhaustive evaluations of RBE using more complex endpoints (ie. angiogenesis, inflammation, etc). The possibility of performing in vivo experiments is very valuable as there is an important lack of in vivo data in charged particle therapy.
- The negligible divergence of the beam to be provided by LhARA is an important advantage for the investigations in spatially fractionated radiotherapy.
- The potentially more stable beams to be delivered by LhARA in comparison with other laser-based systems is a very relevant characteristic to obtain reliable and reproducible results in biology experiments.

In conclusion, LhARA has the potential to drive a change in current clinical practice by increasing the wealth of radiobiological knowledge. This in turn may be used to devise new approaches decreasing the radiotoxicity on normal tissue, while maintaining or even enhancing, the tumour-kill probability.

Paul Bolton

This input is based on March 25 and 31, 2020 review presentations of a pre-CDR developed by the Centre for the Clinical Application of Particles (CCAP) which proposes to develop the first laser-driven hybrid ion accelerator at STFC dedicated to radiobiological studies relevant to particle beam radiotherapy. It is my view that the hybrid case is the general laser-driven case that also wisely reduces laser-driven source requirements to viable near term levels where commercial provision is a realistic option.

Further, precursory to development of the laser-driven radiotherapy facility, there is much new requisite radiobiology and associated new accelerator technology that must first be explored in detail in research campaigns on the global scale. Also, the LhARA team is right to identify that for both in vitro and in vivo research a dedicated facility is necessary; one that cannot be hampered by daily clinical treatment or other operational constraints. Although it has taken about two decades, the time has come for a proposal of this sort.

This pre-CDR describes in adequate detail a “Laser-Hybrid Accelerator for Radiobiological Applications” (LhARA) which is a programme aimed at accomplishing these general goals in a two staged, ten year strategy. I enthusiastically welcome this proposal.

It is clear that beam delivery (at low and high energies) must offer flexibility to accommodate envisioned as well as unanticipated research priorities and directions in this exploratory realm. So, adaptivity must also be an important feature of a programme like this. Note that FLASH radiotherapy had not yet been discovered when the laser-plasma community was proposing laser-driven radiotherapy machines about a decade ago. Because fundamental radiobiological (and perhaps radiochemical) research requirements are topically broad, it is critical that studies of such be conducted collaboratively and/or cooperatively on a global scale. *I recommend strongly a commensurate and exemplary level of global connectivity and cooperation for the LhARA programme and that embryonic steps toward this ideal situation be explicitly indicated where possible.* Appropriately, LhARA team members have already made suitable reference to this in their general description of planned radiobiological research.

The choice of STFC as the integrating site brings infrastructural advantages; particularly regarding building standards, a multi-disciplinary research environment with skilled personnel, radiation shielding and a range of safety measures. Concerning the hybrid prototype, it is important to note that the LhARA prototype is not expected to be optimally compact or inexpensive; it is expected to be a reliably functioning and versatile prototype that trail blazes new and relevant science.

The LhARA beamline footprint (given as ~ 140 m2 and beam length ~ 22 m without the laser) needs to include the laser system footprint. Although 100 TW lasers might be getting progressively smaller, their system footprints are still significant.

The FFA choice as post-accelerator brings distinct advantages that are described in the March review. I suggest that, given adequate programme successes, the issues of hybrid system size and cost minimization are separate matters to be addressed later with appropriate engineering skill (this could be explicitly stated in the pre-CDR). The LhARA hybrid also serves to further promote the laser-driven case in a more realistic scenario. At last, we need to know definitively the extent to which the laser-driven case can expose new

science and responsively usher new technologies that will both exploit these new findings and provide an R&D testbed; notably for development related to particle beam radiotherapy aimed at cancer cures.

I have assumed that the pessimistic budget level of 53 million pounds includes adequate contingency associated with R&D challenges and other risks.

Findings and comments on the individual talks

Radiobiological motivation

Comments (Paul Bolton)

To justify the cost, this part of the LhARA programme must address the critical issues relevant to both laser-driven accelerators and particle beam therapy. Beginning as early as possible and proceeding in parallel with LhARA, pre-Stage 1 beam line development at existing facilities like Clatterbridge and Birmingham is critical not only for the research but also for establishing early the large scale team that will be essential. Examination of the specified endpoints, exploring 3D spheroid samples, and quantitative hypoxic investigations are essential. It is important to point out where RBE (which depends on many factors) is and is not a useful quantity indicative of more realistic dose profiles and overall PBT efficacy.

Also, FLASH radiotherapy needs further professional scrutiny and definition at molecular and cellular levels. LhARA will address these issues in controlled studies of LET effects, the oxygen role, photons vs ions, etc. LhARA is well-poised to further explore microbeam radiotherapeutic effects that also need to be corroborated. The technology for microbeam production is at an embryonic level.

I have already stated the importance of engaging in a global effort with these fundamental studies. Engaging with the “International Biophysics Collaboration” is consistent with this aim. A review presentation has already stated that the biomedical team for LhARA is under development. We can further ask,*”Can we identify (at least in part) a critical larger scale agenda that can be cooperatively addressed by member laboratories of suitable global consortium?”* In such a case, the LhARA role can be highlighted according to what the laser-driven hybrid accelerator system enables in the UK.

In general, can researchers at this stage specify any development areas that can be good prospects for industrial collaboration ? Ultimately, at the CDR level, what are some of the impactful outreach activities from which both LhARA and affected communities can benefit ?

Laser driven proton and ion source

Findings

- There is long-term experience of Laser driven sources. The Sheath method is well understood. 15 MeV looks comfortable.
- 10 Hz <25 fs, energy < 1% RMS - good
- Reproducibility is key - the characteristics of the beam coming from the source must stay within a tight envelope.
- Tape (Myler) as the target - well established technology but not in this context. Important that tape is at the right place (small focal point), is flat. Follow-up required and foreseen.

- Possible use of machine learning to perform optimization at 10 Hz - would seem an appropriate Use Case
- Diagnostics required at this repetition rate

A faster pulse rate was suggested but this would get expensive quickly apparently. Could be useful to probe this limit.

Comments/Recommendations (Paul Bolton)

The LhARA strategy calls for a commercially provided ~ 100 terawatt (TW) laser system operating at 10 Hz. I agree with basing this approach on more reliable vendor supplied system; rep-rated 100 TW lasers are now routinely available. The hybrid concept affords using this 'relatively' low power (in the present petawatt world) system.

There are key R&D issues associated with the laser system and with the targetry (these systems combined are the laser-driven ion source). One is 10 Hz targetry development that will be key. This must be considered for both protons and carbon ions. Target options have been shown in this review and the expertise of the established 'Target Supply Network' (in which STFC has good representation in some of its founding members) should be closely consulted in this development.

The other concerns the ion energy and here I use protons as example. A 15 MeV operating energy for protons cannot be the maximum (or cut-off) energy (or too close to it) of the proton spectrum in a given bunch. This maximum energy can be highly unstable with a shot-to-shot variation that can be prohibitively large (100%). To optimize stability and reliability one should alternatively consider an 'operating' proton energy that is well below this maximum value. On the other hand operation at a near-maximum energy can minimize angular divergence of the source 'spray' and thereby might improve collection efficiency by the first Gabor lens. So, perhaps with the operation energy there is a trade-off to be negotiated but I think the shot-to-shot volatility of the bunch charge near the maximum proton energy means that it should not be too close to the 'operation' energy regardless of trade-offs.

The latter issue suggests a value in having contingency power in the laser system. I suggest purchasing a laser with adequate plus additional contingency power for general ion source development. This also raises the issue of how the FFA post-accelerator system (injection and extraction lines included) deals with bunch charge variation. Are there beam loading issues that can be problematic?

Review presentation has made reference to machine learning and accelerator control. In the LhARA plans do any such developments pertain to controlling in some way, the laser-driven ion source? Also, I have assumed that much of the essential laser diagnostic cluster is commercially available.

It is my view that cost and size reduction has proven to be a relatively weak mantra over the past two decades of laser-driven accelerator investigations. Apart from making some components of the overall hybrid system as small as can reasonably be accomplished with

proven reliable methods (i.e. without R&D), I suggest ignoring such ambition in favour of developing a smart versatile hybrid prototype that supports a wide range of new investigations. It will likely be neither optimally small nor inexpensive; but let the prototype be prototypical.

The optimal target can be determined by the ion species. Also, it appears that in using Gabor lenses, having only one capture line is practical. To make the point about prototypes and accessibility of multiple ion species, the LhARA team should then consider what is required to have ‘ever-ready’ proton and carbon targetry systems in place for rapid change of ion species. This means a pre-aligned, pre-conditioned proton targetry set up alongside the same for carbon ions such that one or the other can be quickly inserted into the laser focal plane region hopefully without breaking vacuum. Alternatively, this might even be two separate vacuum chambers (each of minimal volume) that can be quickly placed into position. Some minor adjustments to the incident laser path might also be required. No doubt this consideration would be a later stage development once the choices for optimum proton and carbon target types become better established. But, it will be important to show by performance that changing ion species is easy.

Proton and ion capture

Findings

- Gabor lenses (GL) are not widely used. Advantages outlined: a uniform static electron ‘cloud’ produces an ideal focusing electric field; focal length scales with the kinetic energy of the incoming beam; solenoid like, but requires much lower B field for equivalent focal length.
- Penning-Malmberg trap has excellent beam aperture and is designed for high voltage. In this case ~60 kV required - non-trivial, but confident that HV design will be robust. Preliminary HV design shown.
- Preliminary magnet design shown. Magnetic field quality important - use of bucking coils etc.
- Ultra high vacuum required (~1e-10 mbar if possible). Vacuum pump strategy elucidated.
- Differential vacuum between target and capture addressed by differential pumping port.
- R & D Experiment Phase 1 foresees 1st pass plasma lens - Penning Malmberg Trap with 3 ‘floating’ electrodes and options to operate with grounded anode or grounded cathode.
- R & D Experiment Phase 2 foresees 2nd generation plasma lens - outline presented.
- R&D required on low outgassing surfaces, diagnostics
- Stability of electron beam and plasma - potential issues. Numerical simulations in progress.

The team faces a compressed timetable. If the GL approach works, all well and good, If not solenoids offer another solution (options: warm/superconducting; pulsed) - work would need to be done here.

Two main potential issues with Gabor Lens approach:

- High voltage hold-off
- Stability

Recognized and to be addressed in the R&D phase.

Comments (Paul Bolton)

Gabor lens R&D is welcomed. I consider this to be an excellent example of the broader field of plasma photonics (more appropriately plasma ‘ionics’ to avoid confusion with photon applications). With five Gabor lenses planned, this becomes a critical technology with significant investment. The backup plan to use solenoids is therefore necessary.

What is the acceptance angle and therefore the overall capture efficiency for the Gabor lens collector design that LhARA has chosen and how does this compare to a solenoid?

In the next generation (pulsed mode) I assume that the Gabor lens B field (although it is relatively low) might not need to be pulsed. As with the Gabor lens, will the solenoid also be considered for pulsed operation if necessary?

The LhARA team can specify if the 50 mrad divergence in the beam capture region is laser-driven source limited or limited by the Gabor lens aperture. This might affect capture efficiency assessment in that trade-off between proton energy and proton spray divergence at the source.

Design of the LhARA accelerator facility

Findings

Not insignificant accelerator physics challenges. Have to handle from the source:

- Small emittance
- Large deltap/p
- V. small beam size
- V. large divergence
- Space charges
- Mixture of states

Followed by

- Energy selection with collimation
- RF manipulations
- A challenging matching exercise
- Scaling magnetic field manipulations

Alternative design uses quadrupoles to avoid focusing to the spot in both planes simultaneously (which gives some space charge mitigation).

Performance of ensemble still to be demonstrated.

FFA:

Advantages of FFA for medical/radiobiological applications were outlined:
- High/variable dose delivery (high rep rate – 10-100 Hz)
- Variable energy operation without energy degraders
- Compact size and low cost
- Simple and efficient extraction
- Stable and easy operation
- Multiple extraction ports
- Bunch to Pixel active scanning possible.
- Multiple ion capability

Momentum swing and key beam parameters shown. Dynamic aperture looks reasonable from initial tracking studies.

- 10 Hz, variable energy, simple and efficient extraction, baseline septa and kickers parameters shown. Any possibility of increasing the repetition rate to match FLASH effect investigation requirements?
- Big RF swing with magnetic alloy loaded cavities (cf. Finemet at CERN). Not commercially available in particular due to the radial constraints. Need some expertise potentially from other institutes such as KURNS.
- Aimed 1e9 protons per bunch. In particular, regarding the average dose-rate: 51.6 Gy/s for 12 MeV protons (Stage 1), 5.8 Gy/s for 127 MeV protons (Stage 2) and 52.4 Gy/s for carbon ions (Stage 2). Any possibility to exceed 40 Gy/s also for 127 MeV protons (Stage 2), therefore allowing FLASH effect investigations?
- Have to match injection/extraction optics with variable energy - optics claimed to be “quasi-invariable” over required range.
- Only certain discrete energies to be considered - not fully clear what the range and discretization foreseen is.
- Worry about field imperfections and closed orbit distortions, a problem faced by other FFA concepts such as EMMA or the KURNS 150 MeV proton machine. This is crucial in order to envisage a variable energy extraction.
- Worry about how a correction scheme can achieve a zero chromaticity while guaranteeing that the injection/extraction beamlines remain matched to the FFA optics.
- Field correction methods already considered in the preliminary design phase.
- Building on the previous experience and feedbacks from the RACCAM project.
- Note other successful deployment of FFAs (and also some of the issues faced elsewhere)
- Since no scaling FFA with variable energy extraction has ever been built, there is an interest in building a small model.
- Not clear how micro-beam delivery will be implemented

Essential R&D items: the main FFA magnet, and the RF system for the ring

Comments (Malek Haj Tahar)

- Limiting the Bfield to less than 1.4 T is crucial to avoid the iron saturation effects (maybe lower the cost as well) which could lead to a substantial change of the azimuthal field variations when the magnetic field is ramped (to vary the extraction energy). This was an issue in the RACCAM project for instance.
- I believe the correct k-value of the magnet can only be achieved by implementing correction coils along the pole of the magnet, which is already envisioned.
- The flutter function F (in the expression of the magnetic field) is also susceptible to change with the energy (which is a major source of imperfections in previous designs): an active clamp is planned to minimize such an imperfection.

All these points appear to me crucial to demonstrate the concept of FFA with variable energy extraction, which if achieved, will be the first of its kind, I believe.

Comments (Paul Bolton)

For the most part the FFA optics are appropriately conventional and their integrated performance readily simulated. Vertical low energy beam delivery for in vitro studies and horizontal delivery for in vivo studies can support a diversity of experimental configurations at the three end stations. Of the two stage 1 beam designs, the LhARA team might specify the criterion (criteria) for choosing one over the other.

If spot scanning and/or microbeam delivery are to be implemented, will these technologies be imported or will they be developed within the LhARA programme ? As with FLASH radiotherapy, I think there exist a few early reports suggesting novel microbeam benefits that need to be initially corroborated. If these delivery modes are to be developed in the LhARA programme, such planning could be explicitly called out in the full CDR as important developments.

The bunch duration of tens of nanoseconds is short compared to that used in conventional radiotherapy (even in FLASH cases). However, as we know, the intrinsic ‘bunch at birth’ duration for the laser-driven source is significantly shorter and a very distinct feature of the laser-driven bunch. Is there capability with the proposed hybrid system to further reduce the duration of delivered bunches or is tens of nanoseconds the limit in this case? Can alterations be made in the future to post-accelerate the laser-driven source beam even closer to the source or add an upstream chicane? Is the stated few percent energy spread set by a particular beam line optic?

Is the 1e9 protons per bunch delivery to end stations typical at 10 Hz operation? At the in vivo (high energy) end station what technique(s) will be used for x-ray CT irradiation as image guidance ? It might help to specify this if it is already known. Of course, there might be laser-driven techniques based on electron acceleration but proven, commercially available methods are likely preferred.

Simulation of LhARA

Findings

- Bunch parameters enumerated
- Space charge is an issue throughout the cycle - R&D plan to be executed
- Worry about: aberrations from 3rd Gabor lens; octupoles possibly useful. Focus in both transverse planes after third Gabor Lens still a concern
- Excellent agreement between MADX and BDSIM - Excellent agreement between BDSIM and GPT without space charge
- Approx. 70% beam line transmission. Almost all losses in the collimator, minimal secondaries reach end station
- Laser-Target Simulation of Derived Beam results shown. Large distributions at the end station. Magnets set for 15 MeV, significant losses of off-energy particles. More stats required.
- Stage 1 looks reasonable. Further optimization required for Stage 2 in vitro and in vivo beam lines
- Stage 2: Lattice layout and design parameters look reasonable. Further simulations relying on a realistic field map of the magnet and taking into account possible leakage fields as well as realistic imperfections shall be considered to devise a proper correction scheme and demonstrate the design flexibility.
- Space charge dominated beam: matching condition needs to be evaluated for the FFA ring, at least for the low energy part. OPAL is a potential candidate for such simulations.

Well placed to improve models and accuracy (Gabor lens field maps to replace solenoids; RF fields).

Instrumentation

Findings

Use Cases and options outlined:

- Radiochromic films (RCF)
- SciWire - Scintillating Fibre Detector
- Thin ceramic monitors
- SmartPhantom concept - simulations, prototype
- Dosimetry - options
- Laser instrumentation
- FFA Instrumentation: benefit from the expertise of the cyclotron community

Research Plan presented including fast feedback and controls

Lots to do, but solutions and approach seem reasonable.

In particular, the use of planes of scintillating fibers (SciWire) is a valuable approach for online dosimetry, and the development of the SmartPhantom includes interesting solutions.

In general, it is suggested to investigate any possible alternative solution aiming at decreasing the overall uncertainty for both absolute and relative dosimetry. On this concern, the use of radiochromic films (RCF) for calibrating other detectors is surely a robust approach (as RCF are demonstrated to have dose-rate independent response) but not very reliable, as the uncertainties related to dose measurements can be large, respect to the required ones for biological investigations.

A fast and reliable feedback and control system is extremely important, especially with ultra-high dose rates irradiations also characterized by high doses per pulses, which imply an accurate determination of the dose delivered per single shot, in order to stop the system once the prescribed dose is achieved .

Detectors for the measurement of the microdosimetric spectra are also suggested, as the energy deposition at the micrometric scale can provide relevant information to be linked to the biological outcomes. Well-established gas detectors (such as Tissue Equivalent Proportional Counters) are suggested, as well as more practical solid state detectors (such as silicon or diamond microdosimeters).

Comments (Paul Bolton)

Review presentations have made clear the need for online, noninvasive single bunch detection with readout fast enough to keep pace with 10 Hz operation and where necessary to have useable absolute calibrations (for current and dosimetry for example). With nanosecond resolution required, how will initial ion bunch durations be measured?

Examples given for developing diagnostics will be the much needed overall contributions to the instrumentation used in either laser-driven all-optical (i.e. stage 1) or hybrid (i.e. stage 2) accelerator systems. Workshops for highlighting these aspects are being planned. The examples given in the presentation (for example the scintillating fibre and smart phantom) are innovative and quite promising. This technological component will no doubt be ongoing for the duration of the programme; likely pushing beyond examples given in the pre-CDR. The technical instrumentation part of LhARA can utilize other existing facilities but will eventually take increasing advantage of LhARA’s laser-driven hybrid system itself. A helpful point to emphasize therefore, is that the laser-driven hybrid accelerator will continue to be a versatile testbed for new relevant technologies in general; such as instrumentation and beam optics uniquely suited to the laser-driven case.

With an optimistic tone, is it possible to say anything about how some of these new diagnostics might play a role in future machine tuning and control? Also, can envisioned industrial partnerships with instrumentation R&D be identified at this stage? This is a

technical subject area where one might more readily anticipate industrial collaboration. Alternatively, this last issue is possibly more relevant to the full CDR.

Biological end stations

Well understood requirements.

Infrastructure considerations

- Overall layout presented
- Safety codes pertaining outlined
- Initial cost estimate presented with suitable errors. Cost range 22 - 53 MGBP with most likely 33 MGBP. Costing methods for line items range through comparative, parametric, formal quote, budgetary quote to guess.
- Implications of the R&D plan for the Infrastructure and Integration team were outlined.