Pre-CDR Review Input by P.R. Bolton: submitted on April 03, 2020.

General Introductory Comments:

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 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 m^2 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.

The Laser-driven Source:

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.

The Gabor Lens:

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.

Beam lines:

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 chosing 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 benefit 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 importance 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 nanoseocnds 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 10^9 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.

Radiobiology:

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 end points, 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 ?

Instrumentation:

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

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.

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