ERC Advanced Grant 2020

Part B2

Section a. State-of-the-art and objectives

a:1 State of the art

a:1.1 Particle beam therapy

Cancer is a major cause of death with 17 million new cases each year globally and incidence rates predicted to increase to 27.5 million new cases per year by 2040 [1]. Radiotherapy (RT) has a key role in cancer treatment; roughly half of all cancer patients will receive RT at some point during their illness [2]. The therapeutic use of ionising radiation has been guided largely by the goal of eliminating directly all cancer cells while minimising damage to tissues adjacent to the tumour [3,4]. Today, technological advances in radiation delivery, including image guidance and particle-beam therapy (i.e. proton- and ion-beam therapy), have notably improved the conformation of the dose to the tumour, thereby reducing dose to organs-at-risk [3,4]. However, the treatment of some radioresistant tumours, tumours close to a sensitive structure, such as the central nervous system (CNS) and paediatric cancers, is still compromised by the radiation tolerance of normal tissue. The management of radioresistant brain tumours (e.g. gliomas) is especially challenging due to the high morbidity of the CNS.

The Particle Therapy Co-Operative Group (PTCOG) [5] lists 90 proton therapy facilities and 12 carbon ion therapy facilities, based on data published in February 2020 [6]. These facilities are located predominantly in high-income countries. Low- and middle-income countries (LMIC) are relatively poorly served, indeed nearly 70% of cancer patients globally do not have access to RT [2]. It is estimated that 26.9 million life-years could be saved in LMIC if global access could be improved [7]. Novel techniques that are at once robust, automated, efficient, and cost-effective are required to deliver the required scale-up in provision.

Particle-beam therapy (PBT) today is delivered using cyclotrons or synchrotrons. Proton and ion sources in use at cyclotron and synchrotron facilities exploit various forms of plasma discharge [8]. Such sources use high-voltage electrodes to eject protons and ions at kinetic energies of around 60 keV. At such a low energy the mutual repulsion of the ions, the “space-charge effect”, is significant and causes the beam to diverge rapidly as it leaves the ion source. The continuous ion flux produced by such sources may be modulated by pulsing the potential applied to the extraction electrode. Further manipulation of the time structure of the ion flux is performed by the accelerating structure into which the low-energy ion beam is injected. To avoid excessive damage to healthy tissue, the therapeutic dose is delivered over a period of several weeks in a series of daily “fractions” [9,10]. The characteristics of the beams used to deliver PBT is limited by the properties of the cyclotrons and synchrotrons used to accelerate the protons and ions. The use of novel beams with strikingly different characteristics has led to exciting evidence of therapeutic benefit. Examples of such novel techniques include: the delivery of a very high dose in a single fraction (“extreme” hypofractionation) [11]; very high dose rate (> 40 Gy/s, "FLASH") therapy [12], “mini-beam” radiation therapy (MBRT) [13]. Novel techniques that are capable of delivering a variety of ion species, over a range of spectral, temporal, and spatial configurations are required for PBT to realise its full potential.

a:1.2 Radiobiology

The nature of the particle-tissue interaction confers on PBT the advantage that the dose can be precisely controlled and closely conformed to the tumour volume. However, there are significant biological uncertainties in the impact of ionising radiation on living tissue. The efficacy of proton and ion beams is characterised by their relative biological effectiveness (RBE) in comparison to reference photon beams. The treatment-planning software that is in use in the clinic today assumes an RBE value for protons of 1.1 [14]. This means that a lower dose of protons is needed to produce the same therapeutic effect that would be obtained using X-rays. It is known that RBE depends strongly on many factors, including particle energy, dose, dose rate, the degree of hypoxia, and tissue type [15-19]. The radiobiology that determines these dependencies is not fully understood.

Detailed systematic studies of the biophysical effects of the interaction of protons and ions, under different physical conditions, with different tissue types will provide important information on RBE variation that could enhance treatment-planning algorithms and drive the development of personalised patient-therapy strategies.

a:1.3 The Laser-hybrid Accelerator for Radiobiological Applications

I have pioneered the conceptual design of LhARA, the Laser-hybrid Accelerator for Radiobiological Applications [20]. LhARA (see figure 1a) will exploit a laser to create a large flux of protons or ions which are captured and formed into a beam by strong-focusing electron-plasma (Gabor) lenses. The laser-driven source allows protons and ions to be captured at energies significantly above the proton- and ion-capture energies that pertain in conventional facilities, thereby evading the current space-charge limit. The Gabor lenses can provide the same focusing strength as high-field solenoids at a fraction of the cost. Post-acceleration, performed using a fixed-field alternating-gradient accelerator (FFA), will preserve the unique flexibility in the time, energy, and spatial structure of the beam afforded by the laser-driven source. LhARA may be developed in two stages. In the first stage, the laser-driven beam, captured and transported using plasma lenses and bending magnets, will serve a programme of *in vitro* experiments with proton beams of energy of up to 15 MeV. In stage two, the beam will be accelerated to allow experiments to be carried out *in vitro* and *in vivo* with proton-beam energies of up to 127 MeV. Ion beams (including C^{6+}) with energies up to 33.4 MeV-per-nucleon will also be available. Figure 1b compares the energy and estimated maximum instantaneous dose rate of LhARA to the performance of other clinical and laboratory facilities that provide, or plan to provide, proton and ion beams for radiobiology. The beam energy at LhARA has been specified to allow *in-vitro* experiments and *in-vivo* studies using small mammals. The laser-hybrid hybrid approach will allow the unique properties of the laser-driven source—extremely high instantaneous flux in an extremely short pulse over a tiny area—to be preserved and exploited to deliver radiobiological investigations in completely new regimens.

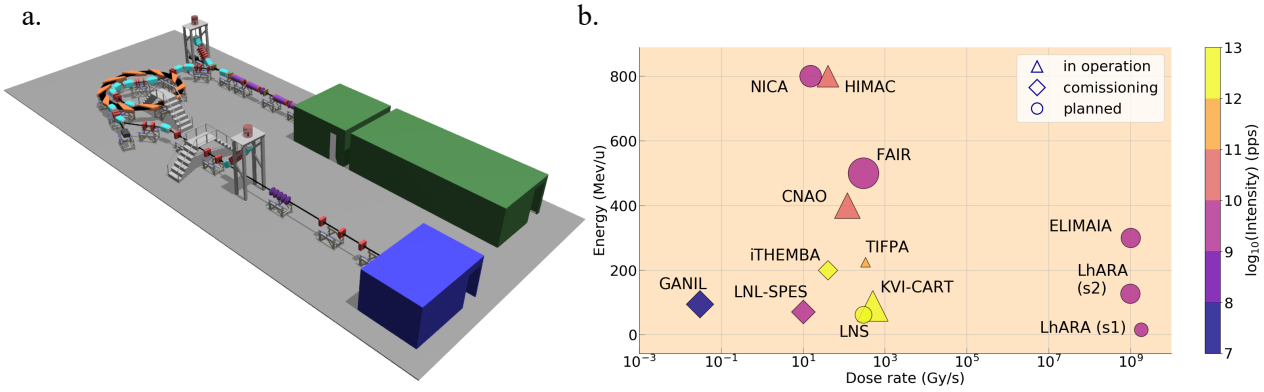

Figure 1: a) Schematic drawing of the LhARA facility taken from the pre-CDR [21]. The laser driven source is housed in the green structures. The stage 1 (s1) beam line is composed of the sequence of Gabor lenses (purple cylinders), dipole magnets (light-blue rectangles), and quadrupole magnets (red squares). The stage 2 (s2) beam line encompasses the fixed-field alternating-gradient accelerator (FFA) ring composed of combined-function magnets (black and orange), and a transfer line leading to the in vivo *end station (dark blue). The* in vitro *end stations are on the first floor (not shown). b) Comparison of the projected performance of LhARA at Stage 1 (S1) and Stage 2 (S2) with the performance of other facilities that provide, or plan to provide, beams for radiobiology [22-40]. The energy of the beam provided is plotted against the maximum instantaneous dose. The range of ion species that are provided by the facility is indicated by the relative size of the marker.*

My vision is that LhARA is a step on the way to the creation of a fully automated PBT system in which the unique features of the laser-hybrid technique are exploited by a feedback system that incorporates time-resolved tissue and dose-deposition imaging to remove the requirement for a large gantry so reducing the footprint of the facility to make "best in class" treatments available to the many. With this proposal I seek the resources to prove the principle of the laser-hybrid technique thereby laying the foundations for the LhARA programme.

a:2 Scientific justification

a:2.1 Motivation for the decision to develop the laser-hybrid technique

Recent advances in the laser-driven acceleration of charged-particle beams make it possible to conceive of new proton and ion sources capable of creating new directions for the exploitation of particle beams for science and society. High-power, short-pulse lasers, which deliver an energy of around a Joule in pulses that are as

short as 25 fs (25×10^{-15} s), are commercially available. Multiple ion species, from proton to carbon, can be produced from a single laser by varying the target foil and particle-capture optics. At source, the laser-driven proton or ion flux is divergent and has a large energy spread. While proton kinetic energies as high as 40 MeV have been produced in the laser-excitation of a foil target [41], the flux produced in the laser-target interaction often varies substantially from one laser shot to the next. A number of initiatives in Europe and across the world seek to deliver laser-driven proton and ion beams with kinetic energies of up to 250 MeV for research [42-44]. I seek the resources to take a contrasting, complementary approach in which the large flux of protons produced at ~15 MeV is captured and formed into a beam, thereby controlling the shot-to-shot variation of the laser-driven flux and preparing the beam for further acceleration.

Conventional ion sources produce ions with kinetic energies of the order 60 keV. At such a low energy the mutual repulsion of the ions, the "space-charge effect", limits the instantaneous dose-rate that can be captured to relatively modest values (of order 10^8 protons-per-pulse, 100 μA [45]). I propose to evade the current space-charge limit using a "hybrid" approach that exploits a series of strong-focusing non-neutral electron-plasma (Gabor) lenses. My hybrid approach will harness the unique properties of the laser-driven source—delivery of a range of ion species (protons to C^{6+}) from a single source in ultra-short pulses that each deliver an enormous instantaneous dose. The successful demonstration of efficient capture and cylindrically symmetric electrostatic focusing will be an important step towards the exploitation of laser-driven ion beams.

a:2.2 Motivation for the decision to target delivery a proof-of-principle system for radiobiology

RT delivered with external sources has been restricted to the same few beam characteristics [9,10]: the same few temporal schemes, low dose rates (<10 Gy/min), beam-particle type (photons are used in 90% of treatments) and spatial distributions (predominantly large beams of several square centimetres leading to homogenous dose distributions). Indications of substantial therapeutic benefit have recently been reported when beams with novel temporal and spatial characteristics have been used. For example:

- *Extreme hypofractionation* in which very high-dose radiation is delivered in one fraction has the potential to transform the immunosuppressive tumour microenvironment resulting in an intense CD8 T-cell tumour infiltrate [46].
- *Very high-dose rate (> 40 Gy/s) FLASH therapy* seems to prevent both activation of the TGF-b/SMAD cascade and acute apoptosis in blood vessels and lead to a reduction of free radical production. These, and other effects related to high dose rate, result in a significant gain in normal tissue tolerance [47] while maintaining the same tumour-control effectiveness. The dependence of the FLASH effect on the beam structure (bunch width, pulse repetition rate, etc.) is yet to be investigated.
- Exploitation of distinct spatial distributions, such as 'mini-beam' radiation therapy (MBRT), activates biological mechanisms different from those involved when direct damage by ionising radiation takes place. MBRT uses a combination of spatial fractionation of the dose and sub-millimetre (500-700 μm) field sizes [48,49]; the irradiation is performed using an array of parallel thin beams. The biological basis of tissue response to MBRT is not completely understood, however, proton MBRT has already been shown to increase the therapeutic index significantly for brain tumours [50].

My pioneering work on the conceptual design for LhARA has demonstrated the potential for the laser-hybrid accelerator technique to be used as the basis of the highly flexible source of radiation required to explore these effects and the vast "*terra incognita*" of the mechanisms by which the biological response to ionising radiation is modulated by the physical characteristics of the beam.

a:2.3 Potential for scientific, technological, and societal impact

My proof-of-principle system has the potential to enhance the two major medical applications of ion accelerators: particle beam therapy; and medical isotope production. The step-change in the clinical practice of PBT that the laser-hybrid technique would allow has been outlined above. Short-lived isotopes for medical imaging are produced at cyclotrons and research reactors. Reactor-based sources have higher capacity than cyclotrons, but are expensive to construct, licence and operate, and produce radioactive waste. Increasing the flux delivered at an accelerator-based source would allow an increase in isotope-production capacity, thereby reducing the need for reactor-based sources.

The laser-implantation of ions using a laser driven source offers a number of advantages in the industrial setting. The laser-hybrid technique I propose offers a route to a low energy (<1 MeV) ion source capable of delivering a wide range of ion species. Other applications of high-power pulsed proton and ion beams also

have the potential to benefit from the removal of the space-charge limit on instantaneous beam intensity at the ion source. The laser-hybrid technique could therefore be developed to enhance the efficiency of large scientific accelerator facilities serving frontier research in the fields such as material science or particle physics which presently exploit "bunch stacking" techniques at high energy.

a:3 Awareness and context

a:3.1 Complementary initiatives to create laser-driven beams for radiobiology

European laboratories have established leading roles in the development of laser-driven sources for biomedical application. A number of groups are investigating the challenges related to the production and capture of ion beams with the desired characteristics. In Germany, the effort is led by the Helmholtz Zentrum Dresden-Rosendorf (HZDR) [51], the Technical University of Munich [52], and Gesellschaft für Schwerionenforschung (GSI) Helmholtzzentrum für Schwerionenforschung [53]. Primary experiments are also beginning at the ELIMAIA-ELIMED facility in the Czech Republic [54]. The ELIMED project has a dedicated programme for radiobiology research based on a laser-accelerated source [55]. At the J-KAREN-P facility in Japan the focus is on developing carbon ions for particle treatment [56]. In the UK Queens University Belfast, Imperial College London, and the Scottish Centre for the Application of Plasma-based Accelerators (SCAPA) collaborate through the A-SAIL project [57] to deliver high-repetition ion beams at energies necessary for deep-seated tumour treatments at about 200 MeV/nucleon.

The initiatives outlined above exploit conventional magnetic quadrupole or solenoid focusing to capture and transport the laser-generated beam. The approach I propose distinguishes itself from these alternative approaches by shifting the focus away from attaining high energies from the laser source and focussing instead on the delivery of a stable and high ion-flux that is captured with high efficiency using strong-focussing Gabor lenses. By emphasising flux stability at production and highly efficient capture I seek to deliver beams with a substantially higher instantaneous dose rate.

a:3.2 The unique advantages of the laser-hybrid approach

The laser pulse that initiates the production of protons or ions in the laser-hybrid accelerator such as LhARA may be triggered at a repetition rate of up to 10 Hz or higher. 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 bunches as short as 10 ns repeated at intervals as small as 100 ms or less. The technologies used to capture, transport, and accelerate the beam in LhARA have been chosen so that this unique capability is preserved.

Table 1: Summary of expected dose per pulse and dose rates that LhARA can deliver. These estimates are based on simulations using a bunch length appropriate for a particular energy ion. The average dose rate is based on the 10 Hz repetition rate of the laser source [21].

	12 MeV protons	**15 MeV protons**	**127 MeV protons**	**33.4 MeV/u carbon**
Dose per pulse (Gy)	7.1	12.8	15.6	73.0
Instantaneous dose rate (Gy/s)	1.0×10^9	1.8×10^9	3.8×10^8	9.7×10^8
Average dose rate (Gy/s)	71	128	156	730

The laser-hybrid technique allows the bunch intensity can be varied by changing the laser-beam parameters. At LhARA, for example, the dose can be delivered in a single 10 ns bunch or over 600 bunches at 10 Hz repetition rate each with an intensity of 10^9 protons-per-bunch. The energy can be varied by collimating the beam delivered by the very strong energy-dependent electrostatic focusing provided by the plasma lenses. This allows beam to be extracted from the FFA post accelerator over a range of energy using methods established by the RACCAM [58] and PAMELA [59] projects. The baseline specification for LhARA has been used in simulations to estimate the maximum dose that can be delivered as a function of energy for protons and carbon ions. A summary of the results is given in table 1. The doses quoted correspond to that which would be delivered to an ionization chamber placed at the position of the Bragg peak. Average dose rates up to 100 Gy/s for protons and 700 Gy/s for carbon ions are possible. The LhARA beam may be used to deliver an almost uniform dose distribution over a circular area with a maximum diameter of between 1 cm and 3 cm. Alternatively, the beam can be focused to a spot with diameter of ~1 mm.

a:4 Objectives

My over-arching objective is to prove the principle of the laser-hybrid accelerator technique by constructing, commissioning, and operating the proof-of-principle system shown schematically in figure 2.

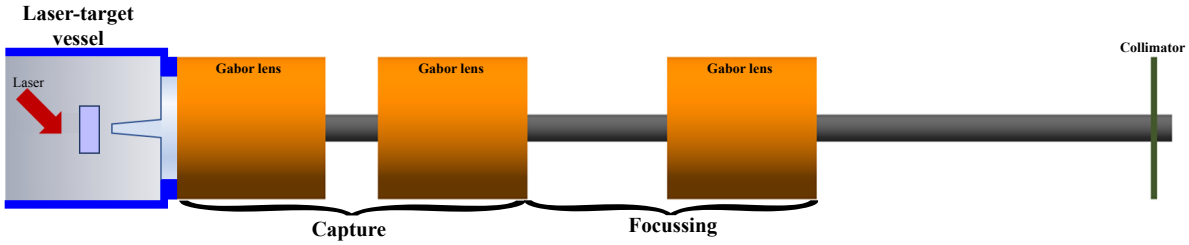

Figure 2: Schematic diagram of the laser-driven target and Gabor lens capture and focussing system. The laser pulse impinging on the foil target is shown by the red arrow. The Gabor lenses are shown as the orange cylinders, the collimator is shown as the vertical green bar. The first Gabor lens is placed as close to the laser-target interaction point as possible. The re-entrant separator between the vacuum in the target vessel and the first Gabor lens is indicated. The first two lenses form the focussing section. The final lens brings the beam to a focus at the collimator.

a:4.1 Composition of the proof-of-principle system

I have conceived the proof-of-principle system in the following functional sections:

Laser-target vessel in which the laser will impinge on the thin foil target to produce the intense proton flux.

I propose to operate in a laser-driven sheath-acceleration (TNSA) regime [60]. The intense, short-laser pulse will be focused onto a target at an angle of 45° to the surface normal. The intense electric field generated on the front surface of the target accelerates surface electrons, driving them into the material. Electrons which gain sufficient energy traverse the target, ionising the material as they go. A strong space-charge electric field, the "sheath", is created as the accelerated electrons exit the rear surface of the target. This field in turn accelerates surface-contaminant ions. The sheath-acceleration scheme has been shown to produce ion energies greater than 40 MeV/u [41].

Key to the operation of this configuration is a system that refreshes the target material at high-repetition rate in a reproducible manner. A number of schemes have been proposed for such studies, from high-pressure gases, cryogenic hydrogen ribbons, liquid sheets and tape drives. I propose to use a tape drive based on the system developed at Imperial College London [41]. This system is capable of reliable operation at target thicknesses down to 5 μm, using both aluminium and steel foils, and down to 18 μm using plastic tapes. Such tape-drive targets allow operation at high charge (up to 100 pC at 15 ± 1 MeV, i.e. > 10^9 protons-per-shot) and of delivering high-quality proton and ion fluxes at repetition rates of up to 10 Hz or more.

Capture section in which intense, divergent proton flux is captured and a parallel beam is produced.

Two Gabor lenses are used to capture the beam and to reduce its transverse momentum to a minimum so that a parallel beam is produced. The first lens must be placed as close to the laser-target interaction point as possible to maximise the capture efficiency. I therefore propose to integrate the first Gabor lens with the laser-target vessel as described below. The position of the second Gabor lens will be chosen based on detailed simulations of the laser-target interaction and the focusing effect of the electron cloud that will be estimated from time-resolved simulations of the behaviour of the electron plasma confined within the Gabor lens.

Focusing section in which the parallel proton beam is focussed to a spot for collimation.

A third Gabor lens will be used to bring the beam to a focus at the position of a circular aperture. The focussing strength will determine the energy of the particles selected. Dosimeters or samples will be placed immediately downstream of the collimator. The energy-selected, collimated beam will be characterised and exploited to make first *in vitro* irradiations of biological samples with the laser-hybrid approach I propose.

The evolution of the beam envelope from the laser-driven source to the collimator is shown in figure 3. The figure demonstrates that the technique I propose has the potential to be used as the injector for LhARA and as the basis of the uniquely flexible, multi-species particle-beam therapy system of the future. However, to realise this potential requires that each of the functional sections be demonstrated and that the overall system be implemented.

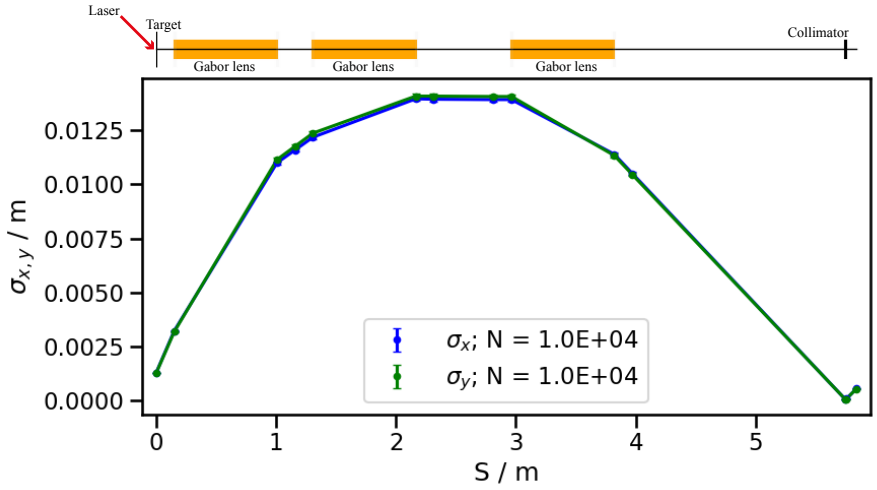

Figure 3: The horizontal (σ_x, blue) and vertical (σ_y, green) beam size plotted as a function of the distance (S) from the laser-target interaction point. The simulation is based on N=10,000 protons from the source. The positions of the Gabor lenses are indicated by the orange bars over the figure.

a:4.2 Principal risks and risk management

The principle technical risks that must be addressed to deliver the proof-of-principle system are:

- Reproducible production of a large proton flux at 15 MeV using the TNSA technique; and
- Production of stable a non-neutral (electron) plasma confined within the Gabor lens.

The integration of the laser-target vessel with the first Gabor lens and the instrumentation required to monitor and characterise the beam also present significant technical challenges.

I have extensive experience of the management of risk in the successful execution of a large scientific project through my leadership of the international Muon Ionization Cooling Experiment (MICE). In this context I was responsible for the construction of the MICE Muon Beam on the ISIS neutron and muon source at the STFC Rutherford Appleton Laboratory (RAL). I was also responsible for the design, construction, commissioning, and operation of the pion-production target and the principle charged-particle tracking devices. As international spokesman for the MICE collaboration I was responsible for the integration of the experiment in the MICE Hall at RAL and led the successful execution of the experiment and the preparation of the results which were recently published in Nature [61].

To achieve the over-arching objective of proving the principle of the laser-hybrid system requires the creation of a project structure that will addresses *ab initio* the principal technical risks. I therefore propose to execute the project through the four work packages defined below.

a:4.3. Work breakdown: objectives by work package

a:3.3.1 Physics simulation

My laser-hybrid accelerator concept exploits the unique properties of two forms of plasma; the first is created when the laser strikes the foil target and causes protons to be accelerated to create the ion flux; and the second is the non-neutral electron plasma confined within the Gabor lens used to produce a cylindrically symmetric focusing force. The critical short-term objective will be to establish a robust simulation capability that exploits existing numerical tools and can be used to optimise the specifications of the target and capture systems.

The processes by which charged particles are produced through the intense electric fields generated as a short-pulse, high-power laser interacts with matter are implemented in a number of computer models. Initial studies of particle production for LhARA have been carried out using the codes EPOCH [62] and SMILEI [63]. Such codes are in routine use in the simulation and interpretation of laser-driven particle-production

experiments. While the TNSA scheme I propose to exploit is well studied, the proposed implementation is novel in that a system that reproducibly produces a high particle flux at ~15 MeV is required. Therefore, to achieve the overarching objective defined above, I will validate the leading particle-production codes with each other and with appropriate data. Developing the codes as necessary, I will exploit the codes to optimise the parameters of the laser-target system. The objective will be to derive an optimised parameter set in the first year of the project. The development and exploitation of the codes will continue to support the characterisation and exploitation of the laser-hybrid source.

Initial time-resolved simulations of the evolution of the non-neutral electron plasma contained within the crossed electric and magnetic fields in the Gabor lens have been carried out using the established particle-in-cell code "VSIM" [64]. These initial studies have shown that the design of the lens must be optimised such that the desired electron density is confined in a stable plasma. The requirement of a stable plasma requires careful optimisation of the design. I will therefore exploit the existing prototype Gabor lens that exists at Imperial College London [65] to execute a programme designed to benchmark the numerical simulation of the electron plasma. Over the first year of the project my objective will be to benchmark the simulation and use it to derive an optimised design for the Gabor lens. The validated simulation will continue to be developed and exploited to support the characterisation of the laser-hybrid capture system.

a:3.3.2 Gabor lens design, build, and validation

A schematic drawing of the Gabor lens I propose for use as the basis of the ion-beam capture system is shown in figure 4. The electron cloud is confined around the axis of the cylindrical vessel by crossed electric and magnetic fields. The field configuration is that of a Penning-Malmberg trap [66] in which a solenoid produces a uniform axial magnetic field over the volume of the long cylindrical electrode. For convenience the central electrode is held at ground potential. Longitudinal confinement is achieved using a strong electric field produced by placing a circular cathode at each end of the anode. An ideal, cylindrically symmetric, focusing force will be produced on a beam of positively charged particles if the charge distribution is uniform. In the thin-lens approximation, the focal length, f, of a lens of length l is given by [20]:

$$f = \frac{\pi\epsilon_0 U}{e^2 n_e} l \, ;$$

where U is the kinetic energy of the non-relativistic positive beam particle, ϵ_0, is the permittivity of free space, e is the electric charge on the electron, and n_e is the electron number density. Such lenses are able to provide strong focussing of high-energy ion beams since the focal length scales linearly with beam energy. My concept for the laser-hybrid accelerator system requires that n_e be approximately 10^{15} m^{-3}. This requires a magnetic field of only 47 mT and a cathode voltage of approximately -65 kV. The magnetic field and the anode voltage may readily be achieved.

Instability of the electron cloud is a concern in the experimental operation of such a lens. Azimuthal beam disruption due to the diocotron instability has been observed and described theoretically [67,68]. The diocotron instability is most problematic under well-defined geometric conditions. My first objective, therefore, will be to use the numerical simulation of the lens to demonstrate a parameter set free from such instabilities. I will then construct a lens prototype and measure its performance to validate the numerical simulation. My objective will be to carry out the successful validation of the prototype lens system in the second year of the project so that the three lenses for the full system can be constructed over the following two years.

a:3.3.3 Laser-target design, build, and validation

My concept for the laser-target chamber is shown as a rendered engineering drawing in figure 5. The tape-drive target is housed in a vacuum chamber that accommodates the laser diagnostics. The target chamber will operate under relatively poor vacuum conditions (10×10^{-5} mBar to 1×10^{-4} mBar) due to vaporisation of the target and outgassing. The Gabor lens requires high-vacuum conditions ($< 10^{-6}$ mBar). I have chosen to implement a differential pumping scheme to avoid the degradation in beam quality that would result if a thin window were used to separate the target-chamber vacuum from that of the Gabor lens. To maximise the capture efficiency requires that the Gabor lens be brought as close as possible to the laser-target interaction point. My design incorporates a 50 mm long re-entrant cone that allows the aperture separating the two vacuum spaces to be reduced to 4 mm so that the required pressure differential can be maintained using reasonably-sized turbo-molecular drag pumps.

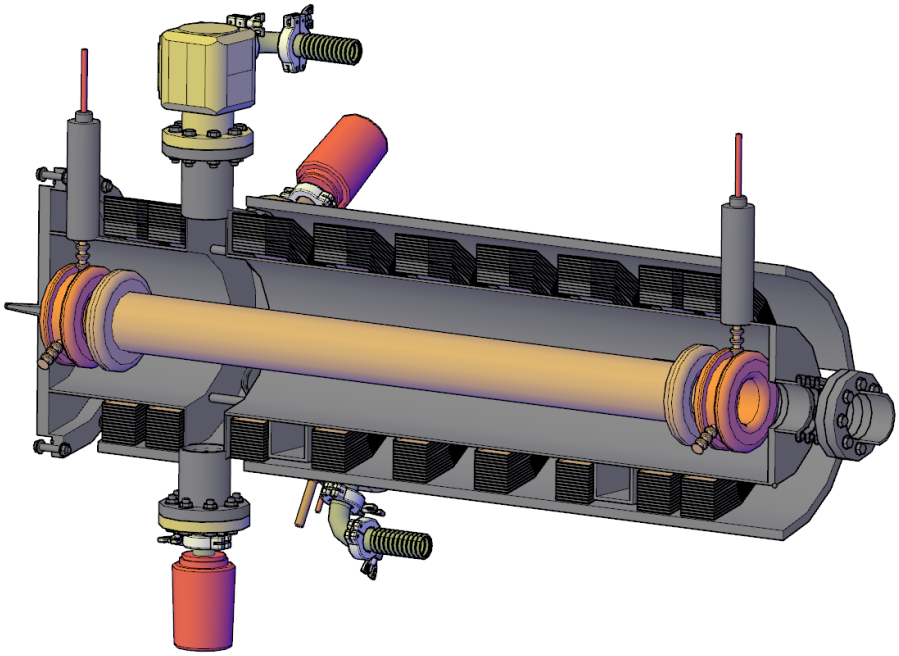

Figure 4: Schematic diagram of the LhARA Gabor lens; the beam enters from the left. The vacuum vessel is shown surrounded by a series of coils that produce the confining solenoidal magnetic field. The central cylindrical electrode is shown held at earth potential. Two high voltage cathode electrodes are shown towards the ends of the vacuum vessel, the connection to the high-voltage feedthroughs is indicated. The diagram also shows the exit flange of the laser-target vessel. The particle-collection cone that points back to the laser-target interaction point may be seen on the left.

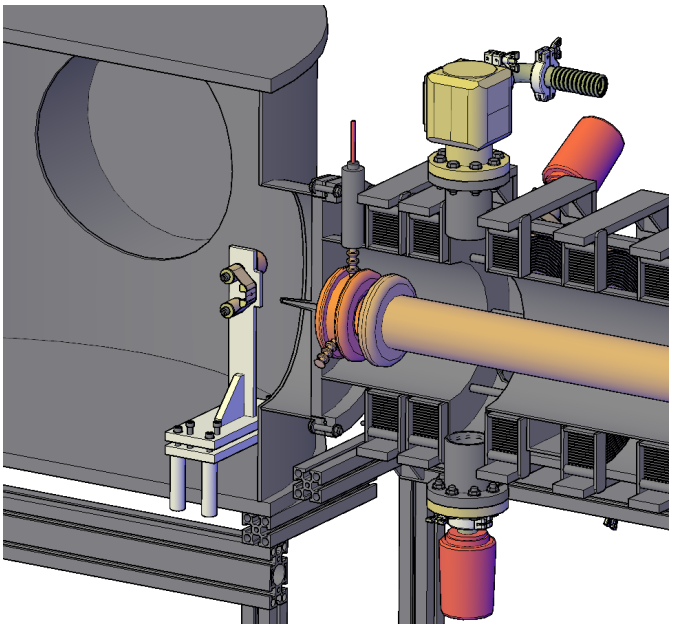

Figure 5: Schematic diagram of the laser-target vessel. The target mechanism is indicated inside the vacuum vessel. The re-entrant cone that accepts the laser-driven proton flux into the capture lens is shown. The cathode electrode and the central anode that contains the electron cloud is shown within the Gabor lens enclosure.

The detailed design of the laser-target chamber will be prioritised during the first year of the project. This will allow the vessel to be installed on the ZHI laser at Imperial College London for measurements of the particle-production rates to be carried out in the second year of the project.

a:3.3.4 Integration, instrumentation, commissioning, characterisation, and exploitation

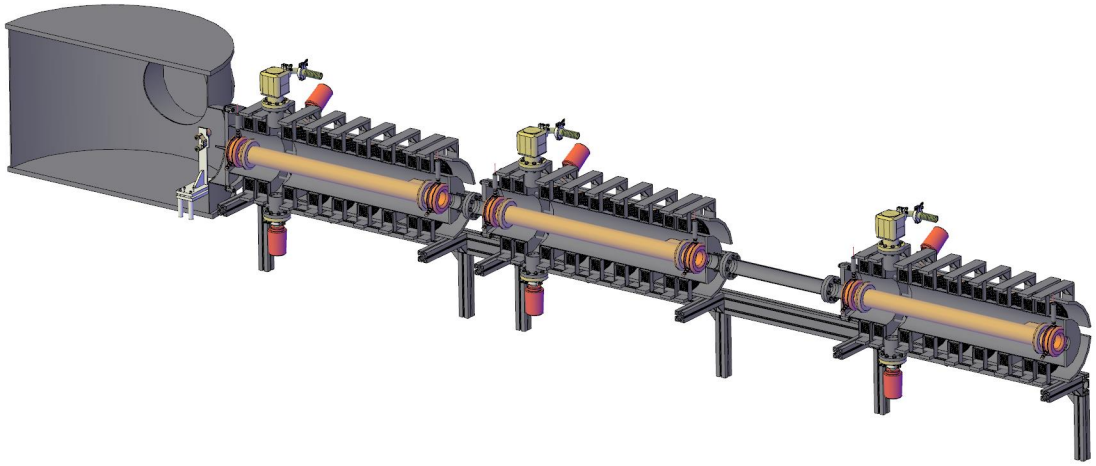

Figure 6: Schematic diagram of the integrated laser-target vessel and Gabor lens capture and focussing system. The figure shows the three-lens system on it supports. The beam pipe through which the beam propagates to the collimator is not shown.

Figure 6 shows a schematic diagram of the system by which I propose to demonstrate the principle of the laser-hybrid technique. The flux entering the Gabor-lens will be measured destructively using a multi-layer pixel detector (such as Timepix4 or HEXITEC) in order to determine, with ~0.1mm precision, the energy spectrum of protons/ions whilst removing the background electron contribution. After the Gabor lens the flux will be measured a single thicker detector plane to measure precisely the focusing capabilities and energy spread. The detector will benefit from newly available edge-less technologies to make a continuous sensor region covering the beam width of dimension 100 mm. Both diagnostic systems will be mounted on a "Roman-Pot" assembly which can be removed from the beam post-diagnostics whilst retaining the vacuum integrity of the system. In collaboration with the National Physical Laboratory, the dose delivered to the samples will be determined through a combination of passive (alanine and Gafchromic films) and active detectors (ionization chambers and calorimeters) appropriately calibrated for the high-dose regimen.

Section b. Methodology

b:1 Overview of project methodology and timeline

Work package	Year 1	2	3	4	5
Physics simulation *Gabor lens, desgn, build, and validation* *Laser-target design, build, and validation* *Integration, instrumentation, commissioning, characterisation, and exploitation*	*Concept validation and detailed design*				
Physics simulation *Gabor lens, desgn, build, and validation* *Laser-target design, build, and validation* *Integration, instrumentation, commissioning, characterisation, and exploitation*		*Prototype construction, evaluation, and refinement of design*			
Physics simulation *Gabor lens, desgn, build, and validation* *Laser-target design, build, and validation* *Integration, instrumentation, commissioning, characterisation, and exploitation*			*Component construction, quality assurance, and characterisation*		
Physics simulation *Gabor lens, desgn, build, and validation* *Laser-target design, build, and validation* *Integration, instrumentation, commissioning, characterisation, and exploitation*				*System integration, qualification, characterisation, and exploitation*	

Figure 7: Timeline for the delivery of the proof-of-principle of the laser-hybrid technique. The four overlapping phases of the project described in the text are indicated by the green bars. The contributions made by the personnel supported by this award through the four work packages described in section a3.3 are indicated.

The key to delivering the proof-of-principle of the laser-hybrid technique with the resources requested here will be the early mitigation of the key technical risks identified above. Therefore, I have adopted a methodology in which the management of risk is prioritised to identify four overlapping phases in the execution of the project (see figure 7). The principal outcomes of each of the four project phases have been used to identify the key milestones. These milestones will be used to measure progress in the execution of the

project. The work that will be carried out in each of the project phases is described and the key milestones are identified in the paragraphs which follow.

***Phase 1:* Concept validation and detailed design (months 1 to 15)**: a detailed end-to-end simulation of the proof-of-principle system will be developed using particle-in-cell and particle-tracking codes. These codes will be used to support and evaluate the detailed design of the laser-target vessel, the Gabor lens, and the full proof-of-principle system. A critical element of the work to be carried out in this phase is the benchmarking of the codes against published data and measurements made using laser-driven particle sources at Imperial College London and the University of Strathclyde.

Critical analysis of the results of the end-to-end simulation is the immediate first step in the mitigation of the particle-production and plasma-stability risks identified above.

Milestones:

M1: month 12: Time-resolved, 2D & 3D simulations of particle production spectra

M2: month 15: Report presenting detailed design of laser-target vessel and Gabor lens

***Phase 2:* Prototype construction, evaluation, and refinement of design (months 9 to 32)**: as detailed designs for the laser-target vessel and the Gabor lens mature, the construction of appropriate prototype components will be expedited.

Evaluation of the Gabor lens prototype will start with vacuum and high-voltage tests. Interferometric measurements of the electron-cloud density will be made, and the stability of the electron plasma will be investigated. The detailed simulation of the lens developed in phase 1 will be used to interpret the results.

The evaluation of the laser-target vessel will begin with vacuum tests. The tape-drive target system will be evaluated, and the durability of the target-drive mechanism will be tested in air and under vacuum before the target is exposed to the laser. The evaluation process will culminate with the exposure of the tape-drive target inside the laser-target vessel to light from the ZHI laser and the characterisation of the particle spectra produced. The comparison of the simulations developed in phase 1 with the measured performance of the Gabor lens measured particle-production rates will be used to inform revisions of the system design.

The improved simulations will be used to refine the end-to-end simulation, enhance confidence in the performance of the proof-of-principle system, and further mitigate the particle-production and plasma-stability risks identified above.

Milestones:

M3: month 30: Laser-target and Gabor lens performance evaluation and design revision complete

M4: month 36: Report presenting revision of detailed design of laser-target vessel and Gabor lens

***Phase 3:* Component construction, quality assurance, and characterisation (months 28 to 54)**: the integration of the functional sections that make up the proof-of-principle system will begin at month 30 when the design revision of the laser-target vessel and the Gabor lens is complete. Component characterisation and particle-flux measurements will be made at each stage of the assembly of the full system. The results of the end-to-end simulation will be compared with the measurements at each stage and appropriate design adjustments and developments of the simulation will be performed.

The incremental characterisation of the beam line and enhancements to the end-to-end simulation will allow decisions to be made to reduce the risk that the proof-of-principle system will not perform to specification.

Milestones:

M5: month 54: Beam line complete, characterisation of beam at point of use complete

Phase 4: System integration, qualification, characterisation, and exploitation: as the third of the three Gabor lenses comes online the quality assurance and characterisation activity of phase 3 will transition to the characterisation of the full beam line. A thorough and systematic investigation of the particle flux, optical properties of the beam line as well as the properties of the beam delivered to the point of use is planned. This process will culminate in the first irradiation of *in vitro* biological samples provided by members of the LhARA collaboration.

The full characterisation of the beam line will culminate in the measurements required to prove the principle of the laser-hybrid technique and the first irradiation of biological samples.

Milestones:

M6: month 60: Final report on activities and achievements ready

b:2. Staff plan

As Principal Investigator and Project Leader I will direct the execution of the project through the four work-packages described above. I propose to recruit three early-career researchers into key roles in the project to create the nucleus of the team that will take the programme forward to realise the vision of the LhARA collaboration. I place particular importance on the creation of an excellent research environment and have therefore recruited international experts who will, under my direction, provide advice to and mentor the early career researchers in the development of the programme.

As PI and project leader I will direct all aspects of the project. Personnel supported by the resources requested here will execute each of the tasks critical to the success of the project. Expertise and effort from others, both from Imperial College and the University of Strathclyde not funded by this grant, but under my direction, will be required for the manufacture of components, the assembly of prototypes, and the assembly of the full proof-of-principle system. Each of the four aspects of the project requires dedicated manpower, namely postdoc(s) directly supported by this grant, and mechanical, electrical, and electronic engineering effort that will be provided by Imperial College London and Strathclyde University. My staff plan by work package is described below.

b:2.1 Physics simulation: [Early-career researcher post 1]

Early-career researcher post 1 (ECR1) will take responsibility for establishing, developing, and maintaining the simulation and analysis environment required to deliver the proof-of-principle of the laser-hybrid technique. Under my direction, guidance and mentoring will be provided by Professor R. Bingham. The tasks associated with this post are:

Phase 1: development of detailed and complete, self-consistent, time-resolved simulation of the proof-of principle system. Simulation of particle production from the target will require the use of particle-in-cell codes such as SMILEI and EPOCH. The simulation of the plasma dynamics within the Gabor lens will require VSIM or an equivalent time-resolved particle-in-cell code. The simulation of the capture and focusing optics will require the use of a particle-tracking code such as GPT [69] or BDSIM [70]. ECR1 will have access to the appropriate high-performance computing facilities at Imperial, the STFC Rutherford Appleton Laboratory, and the Scottish Universities Physics Alliance (SUPA).

Phase 2: exploitation of the simulation suite established in Phase 1 to support the evaluation of the results derived from the Phase 2 prototype-evaluation programme. Detailed simulation of each of the functional sections as well as the full proof-of-principle system will be required during the design-revision process. ECR1 will contribute to the prototype-evaluation programme, contribute to the development of the analysis tools that will be required, and continue to take responsibility for the development of the detailed simulation suite.

Phase 3 and phase 4: the development and exploitation of the simulation suite will continue during Phases 3 and 4. During Phase 4 the emphasis will switch to the exploitation of the results from the beam-line diagnostics to determine shot-by-shot the dose delivered to the instrumentation or sample placed behind the energy-selection collimator plate.

b:2.2 Gabor lens design, build, and validation [Early-career researcher 2]

Early-career researcher post 2 (ECR2) will take responsibility for the development of the Gabor lens and the lens-evaluation measurement programme. Following the design revision in Phase 2, ECR2 will have responsibility for overseeing the manufacture of the lenses to be used in the proof-of-principle system, their commissioning and subsequent characterisation of their focusing properties. Under my direction, guidance and mentoring will be provided by Dr. C. Whyte. The tasks associated with this post are:

Phase 1: development of the detailed design for the LhARA Gabor lens. Engineering design effort will be provided at the University of Stratchclyde and Imperial College London. ECR2 will benchmark and develop the performance of the Gabor-lens simulation tools developed in work package 1 against the

measured performance of the existing Gabor lens prototype and use the improved simulation to evaluate the performance of the LhARA lens as the design evolves.

Phase 2: component manufacture for the lens will be carried out at the University of Strathclyde in collaboration as appropriate with local industry. ECR2 will oversee component manufacture and lens assembly. As Phase 2 progresses, ECR2 will take charge of the commissioning of the lens and its characterisation, making measurements of the electron-cloud density, the focusing effect on a source of α-radiation, low-energy proton beams provided by the University of Birmingham Cyclotron Facility, and ultimately by laser-generated protons at Imperial College London and the University of Strathclyde.

Phase 3 and 4: ECR2 will oversee the construction of the three Gabor lenses and take charge of the quality-assurance programme required to validate all components of the lenses. As the lenses are assembled, ECR2 will take responsibility for their characterisation in stand-alone operation and, subsequently, their commissioning and characterisation on the beam line.

b:2.3 Laser-target design, build, and validation [Early-career researcher 3]

Early-career researcher post 3 (ECR3) will take responsibility for the development of the detailed design of the laser-target vessel, the measurement of the proton flux characteristics at the source, and the integration of the laser- and particle-diagnostics in the laser-target vessel. Under my direction, guidance and mentoring will be provided by Prof. Z. Najmudin. The tasks associated with this post are:

Phase 1: development of the detailed design for the laser-target vessel. Engineering design effort will be provided at Imperial College London. ECR3 will benchmark the particle-production simulation tools developed in work package 1 against published data and measurements that will be made at Imperial College London and elsewhere. The simulation tools will be developed in collaboration with ECR1 and exploited to evaluate the performance of the laser-target and proof-of-principle beam line as the design evolves.

Phase 2: component manufacture for the laser-target system will be carried out at Imperial College London in collaboration as appropriate with local industry. ECR3 will oversee component manufacture and system assembly. As Phase 2 progresses, ECR3 will take charge of the commissioning of the foil-target drive and the characterisation of the particle flux. Measurements made will be used to benchmark and develop the simulation tools and inform the refinement of the design of the system.

Phases 3 and 4: ECR3 will oversee the integration of the laser-target vessel on the Cerberus laser at Imperial College London and take charge of the quality-assurance programme. ECR3 will take responsibility for the optimisation of the particle source as the beam-line integration progresses.

b:2.4 Integration, instrumentation, commissioning, characterisation, and exploitation

The integration of the proof-of-principle system will be performed by engineers and technicians from Imperial College London and the University of Strathclyde. Dr. A. Howard, an outstanding instrumentation scientist, will take charge of the procurement of the laser diagnostics and beam-line instrumentation. Dr. A. Kurup, the Senior Accelerator Project Leader in my group at Imperial, will take charge of the beam-line integration. As the project develops each of the three early-career researchers will contribute to the commissioning, characterisation, and exploitation of the proof-of-principle system. Under my direction, guidance and mentoring will be provided by Dr. J. Pasternak.

Phase 1: Drs. Kurup and Howard will work with the engineering team to devise the overall layout of the proof-of-principle system. This will include the detailed specification of the instrumentation and diagnostics. Dr. A. Howard will take responsibility for the procurement of the components of the instrumentation and diagnostic systems will take place towards the end of Phase 1.

Phase 2: the engineering team at Imperial College London and the University of Strathclyde will support the prototype construction, commissioning, and evaluation activities. Dr. A. Howard will take charge of the commissioning of the instrumentation and diagnostic systems.

Phases 3 and 4: Dr. A. Kurup will take charge of the integration of the proof-of-principle system at Imperial College London. ECR1, ECR2, and ECR3 will all contribute to the characterisation of the functional sections and components. Responsibility for the instrumentation and diagnostic systems will remain with Dr. A. Howard.

b:3 Team structure and competences

b:3.1 Team structure

PI and Project Leader: Professor Kenneth Long

The expertise, roles, and responsibilities of individual team members are summarised in table 2. Two early-career researchers will be recruited at Imperial College London: ECR1 will take responsibility for the simulation suite and support the analysis of the performance of the components, functional sections, and full proof-of-principle system; ECR3 with play a leading role in the design, construction, commissioning, and characterisation of the laser-target system. One early-career researcher (ECR2) will be recruited at the University of Strathclyde and will play a leading role in the design, construction, commissioning, and characterisation of the Gabor lens capture and focussing systems.

Table 2: Expertise and roles of individual team members. All the individuals listed (at Imperial or elsewhere) are either world or leading experts in their field and will work under my direction.

Team member	Expertise	Role
Z. Najmudin	Laser/plasma physics, laser-driven ion source specialist	Mentor and guide in the Laser-target design, build and validation work package
R. Bingham	Laser/plasma theory	Mentor and guide in the Physics, theory and simulation work package
C. Whyte	Plasma device specialist and senior project scientist	Mentor and guide in the Gabor lens design, build and validation work package
J. Pasternak	Accelerator physics and beam-dynamics specialist	Mentor and guide in the Integration, instrumentation, commissioning, characterisation, and exploitation work package
A. Kurup	Senior accelerator-project leader	Responsibility for integration and commissioning of proof-of-principle system
A. Howard	Instrumentation expert and semiconductor device specialist	Responsibility for instrumentation and diagnostic systems.

b:3.2 Team members and competences

c:2.2.1 Team members from Imperial College London

Z. Najmudin has been instrumental in many of the major breakthroughs in the area of laser-driven plasma-based accelerators including; shock acceleration of ion beams, demonstration of self-injection from wave-breaking of plasma waves, production of mono-energetic electron beams in wakefield accelerators, establishing the use of betatron radiation from plasma accelerators as a source of synchrotron radiation, and the use of this radiation for x-ray applications.

J. Pasternak is an internationally recognized accelerator scientist and played a leading role in the demonstration of the ionization cooling technique in MICE. He has experience in accelerator commissioning having worked on LEIR (the novel ion accumulator for LHC at CERN) and on EMMA at the Daresbury Laboratory. EMMA proved the "gutter acceleration" principle in a fixed-field alternating-gradient accelerator.

A. Kurup is Senior Accelerator Physics Projects Leader and has extensive expertise of beam simulations, accelerating structure simulations, detector simulations, data analysis, real-time control and monitoring for accelerator and detector systems. He is LhARA project manager and leads the LhARA simulation effort.

A. Howard is an expert in novel detector technologies and Monte Carlo simulation for the development of systems for particle tracking (both pixels and strips), electromagnetic calorimeters, medical PET, low background dark-matter detectors and homeland-security applications (neutron detection). He is also a developer of the Geant4 simulation toolkit.

c:3.2.2 Team members from other institutes

R. Bingham is Professor of theoretical plasma physics at the University of Strathclyde and holds an individual merit scientist position at the STFC Rutherford Appleton Laboratory, working in the Central Laser Facility. His research, represented by over 400 refereed publications, encompasses plasma accelerators, intense laser matter interactions, inertial and magnetic confinement approaches to fusion energy, laboratory astrophysics and fundamental plasma physics.

C. Whyte has an international reputation in the physics, design, construction, and experimental demonstration of novel high-power amplifiers and sources including novel high-brightness electron-plasma sources. He was MICE Project Manager in the crucial design, manufacture, installation, and commissioning phases. Dr. Whyte's current work includes studies of parametric wave coupling in plasmas and broadband high-power amplifiers for radar tracking and identification of space objects.

b:4 Project management

b:4.1 Laser-hybrid accelerator proof-of-principle system design and build project

I shall manage the project through the four work packages defined above. There is considerable linkage between the work packages, therefore clear assignment of responsibilities, good co-ordination, and excellent communication will be essential for the project to succeed. As the design work progresses, I will therefore ensure that my team produces appropriate interface documents describing the demarcation of responsibility. These documents will be updated and reissued as required. The project will be managed through regular meetings of the project team, both remote and in person, with scheduled updates and design "freeze" points agreed by all members of the team and associated with the milestone reports detailed below.

The project is scheduled with an initial focus on modelling and simulation. The first task will take the laser-target parameter set established in the LhARA pre-CDR [21] and develop a 2D model to provide detailed information on the time-dependant particle fluxes from the laser-driven ion source. This data will then be converted into a 3D description of the predicted ion beam, which will constitute deliverable M1. M1 provides the essential input parameters for the capture system and therefore documents a key part of the system performance.

The beam flux and divergence parameters determined in the LhARA pre-CDR define a set of requirements for the novel Gabor lenses and provide an initial set of dimensions which will be used as the basis of the work required to deliver both M2 and M4. A fully 3D particle-in-cell (PIC) simulation of the capture system will be developed from these dimensions. The completion of this work will constitute deliverable M2. The 3D PIC simulation will be a key tool used throughout the remainder of the project to study plasma instabilities, their suppression, and to predict the focussing effect expected from the Gabor lenses.

The final thread of the simulation effort will be to use the established 3D beam-tracking software tools to simulate the propagation of the proton beam through the beam-transport system from the capture point to the beam-delivery point. The Gabor lenses will be simulated from their 3D magnetic and electric field maps with results cross-checked against the results of the full PIC simulations developed to deliver M2. This step is necessary as 3D PIC simulation of the entire beam line is not viable. The tracking codes will include simulation of the instrumentation that will be used. The full simulation will therefore support the test and characterisation efforts planned for the first Gabor lens. A full set of simulated test results will be made available for comparison with the experimental measurements (deliverable M3).

The Gabor lens design will specify the detailed design of the first lens integrated with the laser-target vessel and the detailed design "envelope" of both subsequent Gabor-lens systems. This envelope will be the key interface document for M5 as it defines the dividing line between the capture system and beam-transport system. It is necessary to fix this specification relatively early in the project so that procurement of the major experimental components can progress in a timely manner.

Milestones 2, 3 and 4 will be a key to providing the specification for the procurement of the principal components of the proof-of-principle system: the laser-target vessel and Gabor-lens capture and transport assembly. I will initiate discussions with potential suppliers early so that a detailed understanding of the competing requirements of the various components of the system can be gained. The design reports and specification documents will include the integration of beam diagnostics. I will manage the design and specification documents as "living documents" with an agreed schedule of regular update and re-issue at six-month intervals until the contract for manufacture is placed.

At this point in the project the major design decisions will have been taken and the project moves to the implementation phase.

b:4.2 Project-team cohesion and development

I place particular importance on establishing an excellent, well integrated, and expert team that can take forward the programme initiated through this award. Through my team building activities at Imperial and in

the international MICE and LhARA collaborations I have a reputation for building cohesive and effective teams. The team of world-leading researchers I have recruited to guide the early-career researchers in the execution of the project each have excellent mentoring track-records.

Significant contributions to the project will be made at Imperial College London and at the University of Strathclyde. To ensure that a single project team is forged I will instigate a weekly meeting of the whole project team. Each month these meetings will be held in person and the venue will alternate between Imperial and Strathclyde. Meetings in the intervening weeks will be via video conference.

I will ensure that each early-career researcher has the opportunity to attend appropriate schools and conferences and the opportunity to present the status of the activity and the results of their work at national and international conferences. The publication plan presented below will ensure that the early-career researchers obtains at least four peer-reviewed publications over the duration of the project.

Imperial College London and the University of Strathclyde are both signatories to the "Concordat to Support Research Integrity" and are committed to maintaining the highest standards of rigour and integrity in research. In addition to the academic training outlined above, I will ensure that the whole of the project team receives research-integrity training.

b:4.3 Publication and outreach plan

Significant reports are required at each of the principle project milestones defined above. New material in the fields of laser-hybrid accelerator design, simulation technique, beam-line implementation, beam characterisation, and/or radiobiological observation will be available. I therefore plan to prepare at least one publication in association with each of the 6 project milestones.

Peer-group outreach is planned through presentations at national and international conferences. To maximise the potential for the proof-of-principle demonstration of the laser-hybrid technique to become the springboard for LhARA and to lay technological foundations of a step-change in clinical capability it will be necessary to reach out to clinicians, radiobiologists and patients as well as the public and decision makers. I have co-opted two representatives Imperial Patient and Public Involvement (PPI) Group to the LhARA Steering Group. An encompassing outreach and public-engagement strategy is being prepared by the PPI representatives for presentation to the Steering Group. I propose to build on this strategy and enlist the support of the Steering Group to deliver an energetic and effective outreach programme during the course of the work proposed here.

b:5 Project's legacy; springboard to a step-change in capability

The award of this grant will allow me to prove the principle of the laser-hybrid acceleration technique. The direct outcome of this demonstration will be the establishment of a new technique for the creation of high-flux proton and ion beams for a wide variety of applications.

The operation of the proof-of-principle system, and in particular the execution of the first *in-vitro* exposures, will pave the way for the development of LhARA, the Laser-hybrid Accelerator for Radiobiological Applications. In my pioneering work on the conceptual design of LhARA, I established the potential for the laser-hybrid technique to drive a step change in the delivery of beams for biomedical applications. I will therefore use the proof of the principle of laser-hybrid acceleration technique as a springboard to launch the LhARA project. Through the execution of the LhARA project it will be possible to integrate the laser-hybrid acceleration technique in an automated system that is able to provide multiple ion species over a wide range of dose and dose rate over a wide variety of spectral, spatial, and temporal structures on demand. By integrating this "on demand" capability in a fully automated particle-beam therapy system it will be possible to remove the requirement for a large gantry and so reduce the footprint of the particle-beam-therapy facility of the future.

In summary, the award of the resource requested here will allow me to:

- Establish a new technique for the creation of high-flux proton and ion beams for a wide variety of applications;
- Create the capability to deliver particle-beam therapy in completely new regimens, combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates; and
- Pave the way for the footprint of PBT facilities to be reduced by exploiting the unique flexibility of the laser-hybrid source in a fully automated system removing the requirement for a large gantry.

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