ERC Advanced Grant 2018

Research proposal [Part B2]

*(not evaluated in Step 1)*

**Part B2: *The scientific proposal* (max. 15 pages, references do not count towards the page limits)**

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

Executive Summary

**Lead author:** KL

a1. State of the art

a1.1 Motivation

Cancer is the second most common cause of death around the world. Radiotherapy is used alone or in combination with surgery or chemotherapy in more than half of patients with localised malignant disease. The majority of radiotherapy treatments are delivered using X-rays, electrons or radioactive isotopes. The cells that make up a tumour will be killed if a sufficiently-large dose of ionising radiation is delivered. However, sources of radiation external to the patient necessarily deliver dose to healthy tissue. The central issue for radiotherapy is therefore to maximise the dose to the tumour while simultaneously minimising the dose delivered to healthy tissue.

Modern X-ray therapy facilities exploit a linear electron accelerator mounted on a rotating gantry. Advanced techniques, such as stereotactic beam radiotherapy (SBRT) and intensity modulated radiotherapy (IMRT), have been developed to deliver a dose distribution that is maximised over the tumour volume. State-of-the-art imaging techniques and sophisticated treatment-planning systems are used to determine the dose distribution that minimises dose to healthy tissue and sensitive ‘organs at risk’ (OAR). It is not possible to stop healthy tissues being exposed to radiation since the energy deposited by an X-ray beam falls exponentially with depth (see figure 1a). This characteristic of X-ray beams limits the maximum dose that can be delivered to the tumour without delivering an unacceptably large dose to healthy tissue and OAR. The properties of proton and light-ion (helium to carbon) beams have the potential to overcome this fundamental limitation of X-rays.

The physics of the interaction between ionising radiation and tissue determines the radiobiological effect. Energy loss through ionisation is the dominant mechanism at the energies that pertain to proton or ion-beam therapy. The energy lost per unit distance travelled (the linear energy transfer, LET) increases as the proton or ion slows down. At low velocity the rate of increase in LET is extremely rapid. This generates a ‘Bragg’ peak in the energy deposited at the maximum range of the beam just as the protons or ions come to rest (see figure 1b). In contrast to photons, this characteristic allows the dose delivered to healthy tissue behind the Bragg peak to be reduced to zero for protons (see figure 1a) and almost to zero for carbon ions.

The maximum range, and therefore the position of the Bragg peak, is determined by the properties of the tissue, the beam energy and the ion species. For a particular tissue type and beam energy, the maximum range is reproducible. As a consequence, radiotherapy delivered using proton or ion beams can be tailored to a particular tumour in a particular patient. The localisation of the Bragg peak allows highly conformal treatment plans to be devised. In the case of proton-beam radiotherapy a negligible amount of energy is deposited beyond the Bragg peak. For ions, such as carbon, nuclear processes result in a small amount of energy being deposited beyond the Bragg peak; the energy that emerges being many orders of magnitudes smaller than would be the case for an X-ray beam used to deliver the same dose to the tumour. This effect, combined with the localisation of the energy deposition in the Bragg peak, allows higher effective doses to be delivered using proton and ion beams than with X-rays. To illustrate the potential benefit of treatment using proton and ion beams, figure 1c shows the ‘Tumour Control Probability’ (TCP) for photon, proton and carbon-ion treatments as a function of isoeffective dose.



Figure **?**: (a) **?? Ask Dorothy! ??** (b) Relative inverted dose deposition profile of photons (X-rays, green solid line) and protons (red solid lines). Photons deposit the maximum dose shortly after entry (Depth = 0 cm) after which the dose falls exponentially with depth. Proton (and ions) deposit the bulk of their energy at the end of their range in a ‘Bragg’ peak. Single ‘pristine’ peaks that correspond to a particular beam energy are used to generate a spread-out Bragg peak (SOBP). Reduced dose is deposited before the SOBP and virtually no dose is deposited after the distal end of the SOBP. (c) Dose-escalation for skull-base chordomas (figure taken from **?**). The local control (tumour control probability, TCP) is plotted against the isoeffective dose (for the reference of 2 Gy/fraction) to the target for many clinical trials, using X‑rays, protons, or carbon ions. (d) RBE versus LET from published experiments on in vitro cell lines (figure taken from ?). RBE is calculated at 10% survival, LET values are given in keV/μm in water. Different colours indicate different ions, from protons to heavy ions.

A raster scan is performed to irradiate the full tumour volume. A range of beam energies at each point on the raster delivers dose from the proximal to the distal edge of the tumour. Each particular beam energy results in a single ‘pristine’ Bragg peak (figure 1d); the effect of varying the beam energy is to deliver dose over a ‘spread out Bragg peak’ (SOBP) that is precisely modulated to cover the tumour volume. Treatment planning software must take into account the position of OAR as well as minimising the dose delivered to healthy tissue.

Treatment planning for proton and ion beams is based on the ‘relative biological effectiveness’ (RBE) of particle beams compared to a standard reference X-ray source. For proton beams an RBE value of 1.1 is used. While this value is representative of a variety of in-vitro measurements, it is known that RBE varies across the SOBP and depends on a variety of factors including dose, dose-rate, biological end-point, LET, and tissue type. A recent compilation of measurements of RBE is shown in figure 1d. The RBE of the various ion species appear, broadly, to follow a similar trend as a function of LET. However, the variation between measurements is large and the data is relatively sparse. Uncertainties in the RBE and its dependence on tissue type, LET, ion species etc. directly impact the quality of the treatment plans derived from today’s planning systems. An energetic programme of measurement of the radiobiological effect of a variety of ion species in a single dedicated facility in which sources of systematic uncertainty are minimised is urgently required. The results of this measurement programme will inform the development of a detailed ‘micro-biophysical’ understanding of the mechanisms that determine the RBE. Subsequently, the detailed understanding may be used to enhance the accuracy of treatment planning systems. Such detailed and precise measurements of the radiobiological effect of ion beams are essential for the evaluation of the degree to which radiotherapy delivered with light ion beams is superior to that delivered by protons and/or X-rays.

The ‘in-principle’ advantages of hadron-beam therapy (HPT) have led reviewers to conclude that, if HPT could be made ‘cost-equivalent’ to X-ray therapy, HBT has the potential to replace X-rays for a variety of tumour types and for tumours situated close to the spinal chord or other sensitive organs. This requires that the cost and complexity of the accelerator systems used to deliver the proton and ion beams be reduced. In the long term, laser-driven accelerators have the potential to bring the particle source close to the patient and remove the need for long transport lines and large rotating-gantry systems.

Biological materials have been exposed to laser-driven particle beams, but, to date no laser-driven system has been developed in which a monochromatic proton or ion beam is captured, manipulated and delivered to a biological sample. With this proposal I seek the resources to deliver the necessary proof-of-principle system and to use it to initiate a systematic programme of precise measurement of the radiobiological properties of ionising radiation using a laser-driven source. My project has the potential to establish the development of laser-driven beams as a realistic alternative to the incremental development of conventional systems and a potential route to making charged-particle therapy widely available.

a1.2 Radiobiology to enhance radiotherapy and to drive the evolution of clinical practice

Cell survival and DNA damage will be evaluated in vitro in model systems of candidate malignancies. Recent research showed that the radiation response is not limited to cell death and survival but rather induces cascades of cellular signalling that can potentially be exploited for therapeutic targeting and that PhRT and IBT can induce different signalling events[[1]](#endnote-1),[[2]](#endnote-2) 7,8. In terms of targetable, radiotherapy-induced signalling, immunogenic pathways hold the most promise. It has been shown, that the immune system on the one hand is a major factor during the development of early and late normal tissue side effects and on the other hand, can be exploited for selectively targeting irradiated tumour cells. Particle irradiation appears to be more immunogenic than PhRT, offering an additional parameter of effectiveness 9. In the proposed project, gene expression studies will address this highly relevant objective, elucidating the potential of laser-driven particles to induce immunogenic signalling/cell death as compared to reference irradiation and synchrotron-based acceleration. In summary, the proposed radiobiological research will aim at the advancement of tumour therapy beyond improvement of delivery techniques. The detailed analyses of cellular behaviour in response to different modalities is dedicated to the development of novel tumour targeting as well as normal tissue protection strategies by e.g. selectively inhibiting or stimulating immune effectors.

So far, however, neither is considered during state-of-the-art ion therapy. Regardless of tumour type, microenvironment and fractionation scheme, a proton RBE of 1.1 is assumed. For carbon ions, a variable RBE-weighted dose distribution is used during planning. Neither accounts for individual, biological disease characteristics.

a1.3 Accelerator systems for radiobiology and radiotherapy

Proton and ion beams for radiotherapy and radiobiology exploit a variety of types of accelerator. For example, protons with energies between 10 MeV and 250 MeV can be delivered using cyclotrons which can be obtained ‘off the shelf’ from a number of suppliers. Today, cyclotrons are most commonly used for proton-beam therapy. However, such machines are not able to deliver multiple ion species over the range of energies required for treatment. Synchrotrons are the second most common type of accelerator used for hadron-beam therapy. One advantage of the synchrotron is that the energy delivered to the patient or biological sample can be varied so allowing 3D spot scanning. Designs capable of delivering different ion species have been successfully demonstrated. Synchrotrons are much more flexible than cyclotrons in the range of beam energy that can be delivered. However, the footprint, complexity and maintenance requirements are all larger than for cyclotrons, which increases the necessary investment and the running costs.

The typical injection energy for treatment synchrotrons is in the range of 10 MeV/n. Therefore, since the beam extracted from a conventional ion source has an energy of up to 60 kV, a linear accelerator (linac) is required to accelerate the beam to the energy required for injection. A linac can be designed to accelerate a range of ion species. Since each ion species has a particular mass, and the velocity profile of the linac is fixed by the accelerating structures, a different maximum energy is delivered by the linac for each ion species. Strategies by which the energy variation by species have been successfully tested for the linac. However, as yet such techniques have not been extended to the synchrotron. Efforts to build an proton-treatment facility based on a linac in which the energy of the beam delivered to the patient can be varied are underway. It will be necessary to demonstrate that the linac-based facility is competitive wth respect to cyclotrons and synchrotrons.

The potential to use laser-driven ion beams as the basis for a proton- and ion-beam treatment facility has been under discussion for more than a decade. Today, laser-driven ion sources are not capable of delivering beam-energies high enough to serve a treatment facility. However, such sources have been shown to deliver large fluxes of protons and light ions at the energies required for radiobiological studies. The hybrid laser-driven accelerator proposed here has been optimised specifically for radiobiology could facilitate the use of the hybrid-accelerator technique in other applications and be a stepping stone towards the development of a treatment facility.

a1.4 Instrumentation, dosimetry, data handling, feedback and control

**Lead author(s):** DC, AK **Being drafted.**

a1.4 Existing solutions and motivation for the development of novel capabilities

**Lead author(s):** SG, VB **To be updated.**

To date, numerous proton-therapy facilities are in operation worldwide. Carbon-ion beams for therapy are offered in only 10 facilities worldwide, four of which are in Europe. MedAustron, the Centre for Ion Therapy and Research in Austria[[3]](#endnote-3) is one of these. The relative scarcity of carbon-ion accelerators is due to the significant costs of building and operating a synchrotron capable of accelerating the carbon ions to the energy required for therapy. While light ions, such as protons, can be used successfully for numerous indications, heavy charged particles, such as carbon ions, offer additional advantages. The inverted depth-dose profile of protons allows treatment of malignancies in difficult anatomical locations and has an efficacy approximately 10% greater than the same dose delivered with a proton beam. Carbon ions, due to their heavier mass, have an RBE of 3. Hence, carbon ions can be used to treat conventionally resistant tumours, e.g. pancreatic cancer2,[[4]](#endnote-4). Furthermore, studies reveal a differential regulation of signalling pathways in response to dose delivered using photon, light-ions and heavy ions[[5]](#endnote-5),[[6]](#endnote-6). The potential therapeutic exploitation of a differentially regulated irradiation response in terms of particle species is currently the focus of the radiobiological research group at MedAustron. MedAustron has a dedicated research irradiation room. Proton beam energies of up to 800 MeV and carbon beams with energies up to 400 MeV/u can be delivered to the research room. Vital control experiments can be delivered at the MedAustron research room which contains a 200 kV X-rays source in addition to the proton and carbon-ion beams.

a2. Objectives

a2.1 Overview

**Lead author:** KL

a2.2 Capability for radiobiology

Laser-driven particle acceleration can be the next step towards precision medicine. As with any novel modality, efficacy and safety have to be ensured. Hence, both factors will be evaluated in great detail and in comparison to a) reference X-ray irradiation and b) synchrotron-based particle acceleration. The proposed research unit therefore requires standard radiobiology laboratory equipment to facilitate in vitro research. This includes standard cell culture and molecular biology equipment.

To date, radiobiology research is almost exclusively located at university hospitals and radiotherapy facilities. Inevitably, the access to the most important requirement of particle radiobiology, the ion beam, is limited in these settings as patient treatment and machine maintenance must be prioritized. This proposal aims at building a dedicated research facility. The unrestricted availability of the ion beam to research will therefore attract researchers worldwide. Hence, this facility will continue to drive radiobiology research beyond the initial period, dedicated to comparative studies in terms of safety and efficacy. Over the last years, molecular radiobiology – and pathology emerged from the classical radiobiology as new research fields, aiming at tailoring radiotherapy to the individual patients need. To date, still a static RBE of 1.1 is used for proton therapy, regardless of not only the already well known physical dependencies of the RBE but also oblivious towards biological factors. Although significant advances have been made, particle radiobiology lags behind the technical advances that have been driving this field over the last decade. An improved understanding of a) biological factors influencing the RBE of particles and b) the differential biological consequences of particle treatment in comparison to photon treatment will potentially foster the development of individual, effective and safe therapy regimen. Discoveries in terms of iontherapy- associated differential gene expression, protein- and microenvironment modification and differential systemic effects, e.g. increased immunogenicity, are being made today and will undoubtedly lead to a new era of particle radiobiology beyond the RBE. In the proposed project, gene expression studies will address this highly relevant objective, elucidating the potential of laser-driven particles to induce immunogenic signalling/cell death as compared to reference irradiation and synchrotron-based acceleration. In summary, the proposed radiobiological research will aim at the advancement of tumour therapy beyond improvement of delivery techniques. The detailed analyses of cellular behaviour in response to particle irradiation foreseen in this project is dedicated to the development of novel tumour targeting as well as normal tissue protection strategies by e.g. selectively inhibiting or stimulating immune effectors.

a2.3 Laser-driven source and capture system

Laser-driven ions have been posited as a source for radiobiological studies for a number of years [refs]. However, until now the ion energies, energy spread, and shot-to-shot reproducibility of the flux produced has meant that such sources were not suitable to serve a radiobiology laboratory. A number of radiobiology experiments have been conducted with laser-accelerated ions. However, these experiments have been limited in scope to a single-shot illumination, either due to low laser repetition rates or the lack of a target suitable for high repetition-rate operation. Most of these experiments have been performed on laser facilities with rapidly shifting priorities and at which the time to install dedicated diagnostics and automated sample control has not been attempted. To date, the ion-flux created using a laser has not been captured and manipulated to produce a ‘production ready’ beam anywhere in the world. The facility proposed here will therefore be unique, allow radiobiological studies exploit the numerous benefits of a laser-driven ion source.

Conventional ion sources are capable of producing ions with energies of the order 60 keV. Space-charge effects limit the ion-current that can be delivered to relatively modest values (of order 100 μA [Osmic2012]). To overcome this limitation, we propose to exploit a laser-driven source operating in a sheath acceleration regime [REFS]. An intense, short-pulse laser is focussed onto a target. The intense electromagnetic field created by the laser ionises the front surface of the target, releasing electrons and accelerating them into the target. With sufficient laser power, the electrons gain sufficient energy to traverse the target, ionising the material as they go. As the electrons leave the rear surface of the target, forming a sheath of negative charge and setting up a strong space-charge electric field. This electric field in turn accelerates ions from the rear of the target. This scheme, at present the most widely studied and best understood, has been shown to produce ion energies greater than 40 MeV/u at the highest laser intensities [REF]. The peak proton energy that can be produced scales with the square root of the laser intensity. Proton or ions with energies up to ~10 MeV can be obtained with relatively modest laser intensities.

The target will be presented to the laser in the form of a tape. It is therefore important that the operation of the tape drive is reproducible. Imperial College scientists have operated tape drives successfully with aluminium and steel foils with thicknesses down to 5 µm Al and with 25 µm thick plastic tapes. Such targets can be replenished readily and continuously replenished and allow pulse intensities of >109 protons-per-shot, corresponding to a charge of up to 100pC at 8.9±1MeV, to be delivered at 10 Hz. For the proton and ion flux to be reproducible shot-by-shot, it is essential that the tension of tape be carefully controlled. The tape must be stretched properly to flatten its surface, without stretching it into its plastic response. Imperial College personnel have designed and implemented tape drives with torsion control and monitoring to maintain a high-quality tape surface.

The scheme I propose is unique. Previous attempts to use laser-driven ion sources for radiobiological applications have been performed in single shot configuration, with high latency diagnostics. Use of laser driven sources in other applications have also used low repetition rates most often because of the lack of an appropriate target to generate the ion flux or the difficulty of forming the material under investigation into a target for the ions. Finally, most of the previous attempts have been performed either using low repetition rate laser systems or on laser facilities with rapidly shifting priorities, where the time to install dedicated and automated diagnostics and control has not been available. The system I propose therefore offers a number of opportunities to push the frontiers in the field of laser-driven ion acceleration, in sustained high frequency ion generation, advanced targetry and active, high repetition rate diagnostics. The successful development and execution of such methodologies would, without question, provide a step forward in terms of capability for the field and open up the exciting new opportunities for applications not just in radiobiology, but also medical isotope production and materials processing. The target and diagnostic solutions which will be developed through the project will provide a step change in the possible laser-driven ion experiments and applications.

Similarly, the flexibility of these laser sources in terms of the continuous spectrum of ion energies available, and variable species selection provides a uniquely capable source for radiobiological studies; something traditional sources cannot provide. This includes systematic studies of the radiobiological effects of so called “ultra-high” dose rates; it would be expected fluxes in excess of the ~100Gy total irradiation dose for a tumour can be produced in a single shot. These features, along with the extremely high current beams which can be produced result in a singular source solution which can provide unprecedented levels of flexibility for radiobiology experiments.

The particle beam delivered by the Laser-driven ion source is in general of high quality with a very low emittance. At the same time the beams feature a comparatively large divergence angle, a huge energy spread and space charge forces. While the energy spread will dilute the beam ion density and reduce the space charge forces over a short drift, the large initial divergence requires a significant focussing strength in the first lenses to capture the particles and form a beam that can be transported through the following lattice. Due to the cylindrical symmetry of the beam, quadrupole lenses are only able to capture a fraction of the beam ions in one transverse dimension, limiting the overall capture efficiency. Solenoid lenses on the other hand side would need to be superconducting to allow for efficient capture. Therefore, it is foreseen to use two space charge lenses (Gabor lenses) each using a non-neutral plasma to capture the beam ions and prepare the beam for further transport. The capture angle is expected to be above 50 mrad. The lenses will run with voltages up to 65 kV and magnetic fields up to 0.03 T.

a2.4 Beam transport and beam delivery system

**Lead author(s):** JPa

The unique properties of the flux of ions created by the laser-target interaction must be formed into a beam that can be manipulated to deliver the dose profile required for radiobiological studies in-vitro or injected into a post-accelerator. This section describes the design of the beam-transport and beam-delivery systems that are proposed to deliver the beam to the in-vitro radiobiological end-station.

The ion beam at the target inherits its size from the laser which has been focused to a very small spot with a diameter of ~1—5 m. The ion flux emerging from the production target is highly divergent. To capture a sufficient fraction of the ion flux requires a strong focusing device; either a high-field superconducting solenoid or a Gabor Lens. The capture system proposed here exploits a Gabor Lens to capture the beam, the details of which have been described in the previous section.

The role of the capture section is to reduce the divergence of the beam, while keeping the beam size manageable. It is assumed that the Gabor Lens will transform the point source into a parallel beam. This perform point-to-parallel transformation creates a relatively wide beam that is characterised by a very large betatron function. This beam needs to be manipulated (‘matched’) to reduce the beam size, while keeping the divergence under control, using series of quadrupoles magnets. In addition to the manipulations of the transverse phase space, RF cavities may be placed downstream of the Gabor Lens to perform longitudinal phase-space rotation to increase the beam intensity within the energy acceptance of the ion-selection section that follows.

The ion selection section, located downstream of the matching quadrupoles, has two main goals: to select the narrow energy range of the beam required for precision studies of RBE, typically assumed to be about ±2%, and to separate a single particle state. The baseline target solution is based on plastic tape irradiated by the laser beam, which means that protons and carbon ions in various charge state are created simultaneously. While it seems ideal as a source for the facility, creating both particle species, there is a clear need to separate them for the irradiation studies. Firstly, particles with different magnetic rigidities are separated by introducing vertical bending magnet, which will generate beam dispersion and the correlation between beam energy and position. A collimator is then used to select the required energy band. However the beam will still contain a variety of different particle species or charge states, so, following the collimator, a Wien filter is introduced, which uses a combination of electric and magnetic fields to separate particles traveling with different speeds. The combination of momentum selection followed by velocity selection effectively slects a single ion species effectively purifying the beam. A second vertical dipole will bring the dispersion to zero as the correlation between beam position and energy is unwanted at the irradiation point. The second dipole also brings the total deflection angle to 90 degrees turning the beam vertically downwards as required for the radiobiological studies. The final set of quadrupoles will set the final beam size for the in-vitro studies in the range of 1 mm to 1 cm in diameter. An additional RF cavity may be used to control the bunch length. The preliminary layout of the beam transport system for in-vitro radiobiological studies is shown in figure **?**.

The in-vitro beam system will need to be equipped with several beam diagnostic devices to measure precisely beam position, profile and beam intensity. This will firstly inform the beam commissioning and operation to allow to tune the machine to the design performance and secondly to allow a precise dose calibration for the radiobiological studies. Beam position and profile monitors, beam transformers will be placed in several places along the beam transport line. Information gathered from the diagnostic devices will allow to set the tune for quadrupoles, dipoles, collimators and several corrector magnets to define the beam properties.

The beam transport line outlined above can also serve as the source for the in -vivo studies, which are considered as an option for the next stage of the facility. The beam for the in-vivo studies will be diverted following the particle selection and sent into Fixed Field Accelerator (FFA), which will further accelerate the ion beam to proton equivalent maximum energy of 75 MeV. The beam will be then extracted from the FFA machine and sent to the in-vivo irradiation box.

**Section b. Methodology**

b2 The project structure

**Lead author(s):** KL, VB

b3 Project plan by work package

b3.1 Laser-driven particle source

**Lead author(s):** OE, ZN

The construction of the laser-driven proton and ion source will be carried out in three phases: procurement; installation and commissioning; and operation.

Procurement:

A commercial laser system will be purchased to form the basis of the proton and ion. The procurement process will be initiated on approval and will be carried out over the first **?** months of the project. The procurement will include:

*i. The laser:* The specifications for the laser are:

* Peak power of at least 15 TW in a short pulse (~35 fs);
* Repetition rate of at least 10 Hz with an energy stability at the 1% level with high laser contrast.

A number of supplies offer titanium-sapphire (Ti:Sap) based lasers capable of meeting these specifications. The final choice of supplier will depend on negotiations with the relevant commercial partners and the final costs quoted during the tender process.

The specification of a minimum peak power of 15 TW arises from comprehensive particle-in-cell simulations using the EPOCH code [REF]. These simulations have shown such a system is required to deliver a significant flux of ~10 MeV protons. If, at the time of purchase, the suppliers offer a laser with peak power in excess of 15 TW that can be purchased within the budget then it will be possible to increase the proton-beam energies that can be delivered. This would be desirable as it would mitigate the risk of “failed” shots, in which the required peak ion energy is not delivered. The causes of such failed shots typically lie in fluctuations in laser energy and the uniformity of the target tape. The variation in peak energy can be as large as ~10%, so, by operating in a regime away from these extremes, such risks are mitigated. Higher laser powers are expected to be achieved through an increase in the delivered laser energy, a feature which has been shown to yield higher particle fluxes [REF].

ii. Ion-production station:

The ion production station will constitute a dedicated vacuum chamber within which the laser beam to target will impinge on the target. Vacuum transport lines are envisaged from a dedicated laser room to the interaction chamber. This is required to minimise laser-radiation hazards and to allow parallel working. The dimensions of the vacuum chamber (1x1x1 m3) have been chosen to accommodate the tape target, all laser delivery and focussing optics, opto-mechanics and diagnostics required to generate a stable, reproducible proton/ion beam. The vacuum chamber will operate at or below a pressure of 10-6mbar. An appropriate vacuum system will therefore be required.

Installation and Commissioning:

Laser installation and commissioning will be completed by the supplier. A working system will be handed over to Imperial College operating with the parameters specified in the contract and in line with the specifications defined above. Installation of the ion-production station will be conducted in parallel with the laser installation. This work is expected to take **?** months.

Commissioning will follow the installation, and comprise the initial proton generation work and subsequent optimisation of the generated beam. The initial ion beam generation stage will involve full characterisation of the source. The measured characteristics will be used in the end-to-end simulation of the set up so that the capture and transport sections of the facility can be fully optimised. This optimisation stage will deliver the optimal proton/ion spectrum in terms of energy and flux, while remaining in the stable-operation regime of the laser.

The Imperial College personnel have extensive expertise in performing such installations and optimisation studies on laser systems at Imperial College and at national scale facilities worldwide. The commissioning phase is expected to take **?** months.

Operation:

Operation of the system is envisaged to be through the delivery of a stable proton and ion beams at energies up to ~10 MeV at 10Hz.

b3.2 Particle capture

The Particle capture project plan covers the general tasks of the detailed design of the Gabor lenses. This task will, over the first year, inform the project with a detailed specification list on performance parameters and produce a set of design drawings for lens production. The task of the production of the lenses as well as their initial tests off the beam line will dominate the work load in the second year of the project. In the third year, experimental data on the lens performance with beam will be obtained with the goal of being ready for installation on the AHAfRB beam line such that first beam can be delivered to the beam-transport section in year 4. The project plan aims to be ready for routine beam delivery in the 5th year. To achieve this goal in the given time the experiences with the lens existing prototype lens at Imperial will be essential.

b3.3 Beam transport and delivery

A review of the detailed design of the beam-transport and delivery system will be carried out when the parameters of the laser have been determined. The beam-optics calculations and beam-dynamics simulations will serve to optimise the beam line and to predict the beam characteristics at the biological end-station. This work is expected to be carried out during the first year of the project. In parallel the detailed design of the support structure will be carried out and the infrastructure requirements of the project will be determined. The Gabor lenses required by the capture system will be manufactured in house, while all beam-line magnets will be purchased externally, together with their power supplies. The magnet electrical system will be designed by communication with manufacturer and in consultation with electrical engineers at the Daresbury and Rutherford Appleton Laboratories. The magnet system will be integrated with the central control system and the beam diagnostics. The vacuum system will also be designed in consultation with experts from DL and RAL. The beam line installation will be carried out by technical staff from Imperial. Beam commissioning will carried out incrementally as the system is developed.

b3.4 End-station for radiobiological research

**Lead author(s):** SG **To be updated**

The response of malignant as well as normal cell lines to irradiation with a) laser-driven accelerated particles b) synchrotron accelerated particles and 200 kV X-rays will be characterized. Cell lines, highly relevant for ion beam therapy will be chosen.

Cell survival, DNA damage and immunogenic signalling will be characterized as endpoints of interest to crosscorrelate the radiation response in terms of different means of acceleration. Samples will be irradiated at several positions along the depth dose curve with malignant cell lines at multiple positions in the SOBP and normal tissues in the entrance, proximal dose-fall off, SOBP and distal dose-fall off.

Colony formation assays will be used to generate cell survival curves as a basis for the RBE calculations to evaluate the biological effectiveness of laser-driven particle acceleration in comparision to X-rays and synchrotron-based acceleration.

yH2AX as a marker of DNA double strand breaks will be visualized and quantified directly after irradiation and 24 hours later to compare initial vs. residual DNA damage, revealing the cell´s capacity of damage repair in response to different modalities of irradiation.

Gene expression will be evaluated using quantitative polymerase chain reaction (qPCR) with emphasis on immunogenic effectors.

**Milestones:**

M4.1: Equipping the facility for radiobiological research

M4.2: Evaluation of cell survival after reference-, control-, and laser-accelerated ion irradiation.

M4.3: Evaluation of DNA damage and damage clearance after reference-, control-, and laser-accelerated ion irradiation.

M4.4: Evaluation of differential immunogenic signalling after reference-, control-, and laser-accelerated ion irradiation.

b3.5 System integration, diagnostics, dosimetry, data-handling, feedback and control

To ensure efficient and safe running of the radio-biological facility, there is a need for a variety of diagnostic devices and a control system that integrates the laser source, beam line components, radiobiological devices and monitoring of the environment and critical services. The overall running of the experiments is envisaged to be set up from an end-used perspective, i.e. be driven by required dose and dose distribution. The control system then needs to translate those operating parameters into control parameters of the accelerator and the translational stage the target cells will be mounted on. It is therefore important that the control system be designed from the bottom up with efficient system integration as a primary objective.

The controls system consists of three main areas: global controls; slow controls; and fast controls. Global controls include the interface the operator uses to run the experiments and monitoring of the different systems. Slow controls provide the interface to the all the devices that need to be controlled and the devices that provide monitoring information. Fast controls provide safety critical monitoring and control of the different systems with the main objective being to protect equipment. Redundancy will be built into the fast controls to minimise risk of damage to equipment due to the failure of any fast controls. The personnel protection system (PPS) will be provided by the host institute and will be interfaced to the fast controls.

Diagnostics

A variety of diagnostic devices are needed to ensure safe and efficient operation of the facility. This includes diagnostic devices for the beam line, end-station, dose calibration and monitoring of the environment and critical services. The following sections describe the requirements for each of these systems.

Accelerator

To ensure commissioning and monitoring of the beam line, beam current monitors, i.e. a current transformers (CTs) and beam position monitors (BPMs)will be required. It is envisaged that a CT and BPM pair will be placed at four locations along the beam line. These will provide beam intensity and position measurements to allow tuning the beam line to maximise transmission and provide fast feedback to the control system in the case of failure of a beam line component or out-of-range variation of the laser-driven ion beam pulse.

End Station

Diagnostic devices in the end station will be used to calibrate the dose delivered to the in-vitro target using invasive devices: a Faraday cup, dose calibration device, films for energy measurement and a scintillator-based profile monitor. Non-invasive devices will be used to monitor the dose delivered: a CT and a BPM.

Dosimetric characterisation of the proton beam generated by the laser driven source and the dose absorbed by the biological samples will be achieved using a range of passive detectors. Due to the unique and complex specifications of the beam (i.e., high dose rate pulse, relatively small beam size and low energy), conventional dosimetry techniques and detectors (i.e. ionization chambers) cannot be employed in a standard operating mode. Other suitable detector technologies such as Gafchromic films and nuclear-track detectors will be optimised for the specific characteristics of the laser driven proton beam. This will include measuring correction and calibration factors due to quenching of the detector response caused by ionization clustering of the low energy proton beam and the impact of high dose rate on the detector response.

A Faraday cup will be used to calibrate the online beam intensity measurements from the CT and BPM and the profile monitor will be used to calibrate the BPM in addition to providing information about the transverse intensity profile of the beam, which is important for ensuring the dose delivered to the cells is uniform over the whole target.

Environment and services

Monitoring of the environment in the end station and services (such as electricity, water and compressed air) to the facility need to be monitored to ensure correct operation of the different systems. This is mainly to protect equipment (e.g. in the case of component or services failure) and to understand changes in operational conditions (e.g. changes in ambient temperature) that may affect the results of the experiments. Other monitoring includes: radiation in the end station; visual monitoring of the cell target; and oxygen levels in the end station.

The Control System

The control system is divided into three parts: global controls, slow controls and fast controls.

*i. Global controls:*

Global controls provide the interface that the operator will use to run the experiments and monitoring of all the systems via slow controls and fast controls. The operator interface will be designed such that control of the accelerator will be from a radiobiological perspective, e.g. instead of setting magnet parameters the required dose and dose distribution will be specified (as in a treatment plan). These parameters are then translated by global controls (using calibration data) into control parameters of the accelerator.

Global controls will also provide monitoring of the fast and slow controls generating alarms if any parameters go outside their acceptable range. Various parameters will need to be logged to provide an accurate record of the conditions whilst experiments are being run and to provide calibration data. This requires specific hardware (mainly servers, disks and networking) as well as software.

*ii. Slow controls*

Slow controls provide the hardware and software interfaces to all the devices needed to run the experiments. This includes the laser system, all components in the beam line, all components in the end station and all environment and services monitoring devices. Additional software will be needed for special runs such as calibration, commissioning and debugging for system experts.

*iii. Fast control system*

Fast controls provide redundant monitoring of all systems and redundant control of devices (primarily to put devices in a safe state) in the event of a critical failure. This will include an interface to the PPS of the host institute. Redundancy is important in both the controls and monitoring functions of the fast control system to minimise the risk of damage to equipment due to the failure of the fast control system.

b4 Milestone summary

**Lead author(s):** KL, VB

**Section c. Resources (including project costs)**

(Note: State and fully justify the amount of funding considered necessary to fulfil the objectives for the duration of the project. To facilitate the assessment of resources by the panels, the use of the following budget table is strongly recommended. All eligible costs requested, should be included in the budget. **Please use whole euro values only**.)

Justification of resources, team expertise etc.

**Lead author(s):** KL, VB

|  |  |  |  |
| --- | --- | --- | --- |
| **Cost Category** | | | **Total in euro** |
| **Direct Costs[[7]](#footnote-1)** | **Personnel** | PI[[8]](#footnote-2) |  |
| Senior Staff |  |
| Postdocs |  |
| Students |  |
| Other |  |
| *i. Total Direct costs for Personnel (in euro)* | |  |
| **Travel** | |  |
| **Equipment** | |  |
| **Other goods and services** | Consumables |  |
| Publications (including Open Access fees), dissemination activities, etc. |  |
| Other (please specify) |  |
| *ii. Total Other Direct Costs (in euro)* | |  |
| **A – Total Direct Costs (i + ii)** (in euro) | | |  |
| **B – Indirect Costs (overheads)** 25% of Direct Costs[[9]](#footnote-3) (in euro) | | |  |
| **C1 – Subcontracting Costs** (no overheads) (in euro) | | |  |
| **C2 – Other Direct Costs with no overheads[[10]](#footnote-4)** (in euro) | | |  |
| **Total Estimated Eligible Costs (A + B + C)** (in euro) | | |  |
| **Total Requested Grant** (in euro) | | |  |

The project cost estimation should be as accurate as possible. Significant mathematical mistakes may reflect poorly on the credibility of the budget table and the proposal overall. The evaluation panels assess the estimated costs carefully; unjustified budgets will be consequently reduced. The Total Estimated Eligible Costs and the Total Requested Grant amounts in the table MUST match those presented in the online proposal submission form, section 3 – Budget.

In case you are requesting additional funding above the normal EUR 2 500 000, fully justify your request by filling in the table below (please delete the table if not applicable). **Include these costs in the above budget table.**

|  |  |
| --- | --- |
| **Request for additional funding above**  **EUR 2 500 000 for** | **Justification** |
| Keep only the category(ies) that apply to the project.  (a) covering eligible 'start-up' costs for a PI moving from another country to the EU or an Associated Country as a consequence of receiving an ERC grant and/or,  (b) the purchase of major equipment and/or,  (c) access to large facilities. |  |

The requested contribution should be in proportion to the actual needs to fulfil the objectives of the project.

|  |  |
| --- | --- |
| **Please indicate the duration of the project in months:[[11]](#footnote-5)** |  |
| **Please indicate the % of working time the PI dedicates to the project over the period of the grant:** | **%** |

Specify briefly your commitment to the project and how much time you are willing to devote to the proposed project in the resources section. Please note that you are expected to devote at least 30% of your total working time to the ERC project.

1. Jasi K, Pochylczuk K, Michalik M, et al. Proton beam irradiation inhibits the migration of melanoma cells. 2017:1-16. doi:10.1371/journal.pone.0186002. [↑](#endnote-ref-1)
2. Nielsen S, Bassler N, Grzanka L, et al. Differential gene expression in primary fibroblasts induced by proton and cobalt-60 beam irradiation. Acta Oncol (Madr). 2017;0(0):1-7. [↑](#endnote-ref-2)
3. PTCOG. Particle therapy facilities in operation. 2018. https://www.ptcog.ch/index.php/facilities-in-operation. [↑](#endnote-ref-3)
4. Mohamad O, Sishc BJ, Saha J, et al. Carbon Ion Radiotherapy : A Review of with an Emphasis on DNA Damage / Repair. 2017:1-30. doi:10.3390/cancers9060066. [↑](#endnote-ref-4)
5. Chiblak S, Tang Z, Campos B, et al. Radiosensitivity of Patient-Derived Glioma Stem Cell 3-Dimensional Cultures to Photon, Proton, and Carbon Irradiation. Int J Radiat Oncol. 2016;95(1):112-119. doi:10.1016/j.ijrobp.2015.06.015. [↑](#endnote-ref-5)
6. Suetens A, Konings K, Moreels M, et al. Higher Initial DNA Damage and Persistent Cell Cycle Arrest after Carbon Ion Irradiation Compared to X-irradiation in Prostate and Colon Cancer Cells. Front Oncol. 2016;6:87. doi:10.3389/fonc.2016.00087. [↑](#endnote-ref-6)
7. An additional cost category 'Direct costing for Large Research Infrastructures' applicable to H2020 can be added to this table (below ‘Other Goods and services’) for PIs who are hosted by institutions with Large Research Infrastructures of a value of at least EUR 20 million and **only** after having received a positive ex-ante assessment from the Commission's services. [↑](#footnote-ref-1)
8. 3 When calculating the salary, please take into account the percentage of your dedicated working time to run the ERC funded project (i.e. minimum 30% of your total working time). [↑](#footnote-ref-2)
9. Please note that the overheads are fixed to a flat rate of **exactly** 25%. [↑](#footnote-ref-3)
10. Such as the costs of resources made available by third parties which are not used on the premises of the beneficiary (see "Information for Applicants to the Advanced grant 2018 Call" for details). [↑](#footnote-ref-4)
11. The maximum award is reduced pro rata temporis for projects of a shorter duration (e.g. for a project of 48 months duration the maximum requested EU contribution allowed is EUR 2 million). Additional funding to cover major one-off costs is not subject to pro-rata temporis reduction for projects of shorter duration (e.g. with additional funding it is possible to request a maximum EU contribution of EUR 3 million for a project of 48 months duration). [↑](#footnote-ref-5)