LARA Conceptual Design Report: “Template” Proposal

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# Scientific Synopsis

## “Mission Need”

The second most common cause of death globally is cancer, which accounted for 8.8 million deaths in 2015[[1]](#endnote-1). The commonest malignancies are lung (1.69 million deaths), liver (788’000 deaths), colorectal (774’000 deaths), stomach (754’000 deaths), and breast (571’000 deaths). In all of these, local cancer control is of major importance to quality of life and overall survival. The 2012 European Cancer Observatory[[2]](#endnote-2) estimated that radiotherapy is used in half of all cancer patients in Europe[[3]](#endnote-3).

The Directory of Radiotherapy Centres[[4]](#endnote-4) (DIRAC) predicts 4 million new cancer patients in Europe by 2015, up from 3.4 million in 2012[[5]](#endnote-5). An increase of 16% in the number of courses of radiotherapy delivered in 2012 is expected by 2025[[6]](#endnote-6), with larger increases expected for particular tumours. The trend in cancer diagnosis indicates that, by 2035, 26.9 million life-years in low- and middle-income countries could be saved if their radiotherapy capacity could be scaled up**[[7]](#endnote-7)**. Evidence suggests that the investment required to scale up the provision of radiotherapy would generate substantial economic gains as well as reduce the global cancer burden.

Today's stereotactic beam radiotherapy (SBRT) achieves doses and local tumour-control rates well above those that have been achieved in the past. This is illustrated by the outcomes for patients with non-small-cell lung cancer[[8]](#endnote-8). However, despite recent advances in four-dimensional computed tomography (4DCT), intensity modulated radiotherapy (IMRT) and other state-of-the-art photon technologies, the location of primary tumours in relation to heart, lungs, oesophagus and spine limits dose intensity in a significant proportion of cases[[9]](#endnote-9); i.e. the proximity of healthy organs to important primary cancer sites limits the photon-dose intensities that may be delivered.

Proton and ion beams are attractive options for radiotherapyas, in comparison to photons, there is little (ions) or no (protons) dose deposited beyond the distal tumour edge. This saves a factor of 2—3 in integrated patient dose. In addition, as the dose is primarily deposited at the maximum range of the beam, treatment can be conformed to the tumour volume. Proton-beam-treatment planning assumes that the relative biological effectiveness (RBE) is a factor of 1.1 larger than the effect that would be achieved if the same dose was delivered using photons[[10]](#endnote-10). A detailed, micro-biophysical understanding of proton-tissue interactions would allow enhanced treatment-planning systems to be developed that account for variations in RBE with tissue type. In the case of ion-beam radiotherapy, there is a need for robust, measurement-based models of beam-tissue interactions to inform the development of ion-beam treatment-planning systems[[11]](#endnote-11). Therefore, to maximise the benefits of hadron-beam therapy requires a detailed, systematic radiobiology programme to underpin the development of a micro-biophysical understanding of proton-tissue interactions and to determine the radiobiological properties of ion beams with precision sufficient for their biological effectiveness to be simulated with confidence[[12]](#endnote-12).

Increasing the availability of particle-beam therapy requires a reduction in the cost and complexity of the facility. Driving down the cost needs the development of novel accelerator technologies**[[13]](#endnote-13).** The deployment of such technologies will make it possible to scale-up the provision of particle-beam therapy and allow a greater fraction of the European and global population to benefit from it.

Today, proton- and ion-sources produce particles with energies of tens of keV/u. At such low energies, the Coulomb repulsion between the particles that make up the beam limit the beam-current that can be captured and accelerated. Laser-driven particle-production technology can overcome this by injecting protons and light-ions at high-energy (up to 10 MeV) into a strong-focusing particle-capture system. This approach makes it possible to deliver multiple ion species from a single source while overcoming current beam-intensity limitations.

This proposal will prove the principal of the novel technologies required for future therapy facilities by developing a proton- and light-ion-beam radiobiology facility. This approach has a number of advantages. First, the energy required for in-vitro and in-vivo radiobiology is smaller than that required for therapy, substantially reducing the cost and foot-print of the proof-of-principle system. Secondly, the beam-quality that will be delivered by the purpose-built system will be optimised for the radiobiology programme. The legacy of the programme will be the demonstration of the technologies required to drive a step-change in the provision of proton and light-ion-therapy, and a system capable of delivering the comprehensive set of experimental data that is essential to underpin the enhance proton and carbon-ion therapy today, to allow a robust case for the roll-out of ion-beam radiotherapy to be developed, and to form the basis of the particle-beam-therapy systems of tomorrow.

Establishing a laser-driven charged-particle source, coupled to a novel accelerator system delivering beams of protons and ions from helium to carbon, will provide a facility that will serve a definitive programme of radiobiology. These techniques can be scaled-up for use in compact, affordable particle-beam-therapy facilities in the future. This proposal seeks the resources to deliver the first, proof-of-principle, system that will:

* Demonstrate the principle of laser-driven injection of intense shots of high-energy protons and light-ions into a novel strong-focusing plasma lens; and
* Make the first measurements in-vitro of the micro-radiobiological impact of proton and light-ion beams using the unique, high-quality proton and light-ion beams produced.

Successfully delivering this ground-breaking, proof-of-principle system requires that an interdisciplinary approach is taken from the outset. The Centre for the Clinical Application of Particles (CCAP)[[14]](#endnote-14), at Imperial College London, is composed of clinical oncologists, medical physicists, accelerator and instrumentation scientists and radiobiologists with the mission to ‘*Develop the technologies, systems, techniques and capabilities necessary to deliver a paradigm shift in the clinical exploitation of particles*’. The Centre’s personnel are ideally placed to carry out the research programme defined in this proposal.

## Enabling ground-breaking technologies and challenges

Recent advances in laser-driven particle acceleration at Imperial and elsewhere[[15]](#endnote-15) make it possible to conceive of a novel, hybrid accelerator system in which laser interactions drive the creation of a large flux of protons, or light ions, that are captured and formed into a beam. The great advantage of a laser-driven source over conventional sources is that the protons or light ions produced are injected into the first accelerator structure at high energy (up to 10 MeV) with large beam currents possible. The challenge that must be addressed is the capture and focusing of the highly-divergent flux of particles created by the laser to form it into a beam. Efficient capture and focusing may be achieved using a Gabor lens in which an electron plasma is contained by crossed electric and magnetic fields[[16]](#endnote-16). A prototype Gabor lens required for the application proposed here is presently under test at Imperial.

Bringing together these novel technologies, developed in unrelated fields, to demonstrate and exploit a new concept for the creation of beams of low-energy ions is at the heart of this proposal. The successful exploitation of the proof-of-principle system proposed here will drive a step-change in capability for radiobiological research. The proposed programme carries significant technical risk as it includes the proof-of-principle demonstration of key accelerator and detector technologies. A holistic, system-level approach will be taken to the integration of the accelerator, imaging and dose-measurement systems. The innovative work that will be carried out will lay the foundations for the systematic study of the radiobiological effect of proton and light ion beams and has the potential to be developed further to reduce the foot-print, cost and complexity of the particle-beam-therapy facilities of tomorrow.

In Europe, 10 proton-beam-therapy centres are in operation and a number of new facilities are being planned[[17]](#endnote-17). Three carbon- and light-ion-therapy facilities are available. Some particle-beam-therapy facilities provide beams for pre-clinical research. In such facilities, beam-time dedicated to research is restricted by the need to deliver the clinical programme. The beam delivered to the non-clinical research room is similar to that delivered to the treatment rooms. The advantage of this approach is that the conditions that pertain in clinical procedures can be simulated, evaluated and developed. However, for the study of the micro-biophysical processes that determine the biological effect, the use of beams optimised for treatment has the disadvantage that phantoms must be developed such that the Bragg peak lies within the biological sample. Processes such energy straggling and multiple Coulomb scattering reduce the quality of the beam at the sample when the beam is decelerated in this way. Proving the principal of hybrid, laser-driven, acceleration as the basis for a dedicated radiobiological-research facility will pave the way for the development of similar systems for clinical application.

Present ion sources are capable of providing ions with energies of tens of keV for injection into the first stage of the acceleration system. At such low energies, the size of the beam grows rapidly due to the mutual electrostatic repulsion between the ions. The ‘space charge’ effect limits the intensity that can be delivered by conventional sources, and it can be overcome by using a laser to create high-flux pulses of ions at energies of up to 10 MeV that are injected directly the beam-capture system. The beam-capture system will be composed of two plasma (Gabor) lenses to control the effect of space charge. The short focal length characteristic of the lenses will allow the divergent particle flux created by the laser-driven ion source to be captured and focused such that high-intensity proton and light-ion beams can be produced. The proposed combination of laser-driven source and plasma-lens focusing, techniques for which prototypes have been built at Imperial, will allow studies over a wide range of dose-rates to be studied. The dose to the sample will be measured shot-by-shot using novel micro-dosimeters that have been developed at the National Physical Laboratory and a fast feedback system will be implemented to allow the dose-rate to constrained to that specified in the measurement plan.

The beam emerging from the Gabor-lens capture system will be transported using conventional magnetic elements. Two single 1.3 GHz cavities will be used to maintain the time structure of the beam. Laser-driven plasma sources create a range of particle species. Therefore, the transport line must include a Wien filter which exploits crossed electric and magnetic fields to select a single ion species. Commercial Wien filters are optimised for ion beams with energies lower than those that will be delivered by the source proposed here. We will engage with European suppliers to develop a new Wien filter with the performance required for the delivery of proton and light-ion beams for radiobiology.

The capture system will be followed by a beam-transport section that will cancel the chromaticity and dispersion that will naturally arise in the beam. A beam-delivery system will be implemented to bring the beam vertically down into the climate-controlled biological end-station thereby allowing biological samples to be horizontal during irradiation. The beam-delivery system will include elements to allow the spot size to be varied from 1 mm to 30 mm and a scanning system to allow a raster-scan to be executed. The beam-delivery system must be integrated into the design of the end-station. The end-station design will incorporate climate control and include the ability to vary the partial pressure of oxygen to investigate the effect of hypoxia. An automated, computer-controlled system with remote monitoring will be implemented to allow many samples to be irradiated without the need for operator intervention in the radiation area. This will maximise the flexibility of the system in operation and minimise the beam-time lost in sample manipulation. Precise, micro-dosimetry will be incorporated in the end-station to allow real-time monitoring. The dose measurements will be integrated into the real-time monitoring and beam-control system to record the dose delivered shot-by-shot.

An interdisciplinary team such as the CCAP is required to prove the principle of the hybrid, laser-driven accelerator approach to the delivery of charge-particle beams for radiobiology.

## Laser Accelerator for Radiobiological Applications (LARA)

The design for the Laser Accelerator for Radiobiological Applications (LARA) begins with the creation of a flux of **?** cm-2s-1 of protons or light ions with energies of up to 10 MeV/u using a **XX**kW **YY** laser. The ion-capture system will be composed of two Gabor lenses that will each deliver a focussing power equivalent to a **??** T superconducting solenoid. The capture system will be followed by a beam-transport system that will select the desired beam energy and reject unwanted particle species such that the ion-beam purity is in excess of 99%. Once the ion-beam has been prepared the design allows for the unaccelerated beam to be directed to the in-vitro radiobiology end-station or to a post-accelerator. The post accelerator, which will constitute an upgrade to the system proposed here, will exploit a fixed-field accelerator to raise the ion-beam energy to 70 MeV/u. A second high-energy ion-beam transport section will then deliver the beam to an in-vivo experimental facility.

The beam quality that this design can deliver to the in-vitro and in-vivo end-stations is well beyond that which can be delivered by today’s proton and ion beams for radiobiology. Since the beam energy, beam-spot size, dose rate and beam position can each be varied shot-by-shot, an unprecedented flexibility and control will be provided for the radiobiological end-stations. Exploiting this flexibility will require an automated sample-handling system integrated with the diagnostic and dose-measurement systems and a real-time feedback system to control the accelerator parameters. The proposed facility will provide a step change in the precision with which radiobiological experiments can be carried out.

## Workplan

LARA has been designed to deliver definitive systematic studies in-vitro of the micro-biophysical impact of proton and light ion beams. To deliver the scientific return requires the integration of the beam-delivery, diagnostic, dosimetry, sample-control, and feedback systems. To realise the full benefits of the advanced hybrid-acceleration approach requires that each of the novel systems performs to specification. The key issue to be addressed in executing the project is therefore the management of the principal technical risks which include:

* *Laser-driven proton and light-ion source:*
  + The principle of particle production by laser interactions has been demonstrated at Imperial and elsewhere[[18]](#endnote-18). In the present application, the principal risk is that the laser system will not deliver a sufficient flux into the aperture of the Gabor-lens collection system;
* *Ion-beam capture and initial focus:*
  + Plasma-lens focusing elements for space-charge dominated beams have been demonstrated[[19]](#endnote-19) and a prototype lens of the type required for the present application is being studied at Imperial. The principal risk presented by the capture system is therefore that the focusing strength required for the optimal capture efficiency cannot be delivered; and
* *System integration of beam, diagnostics, dosimetry and biological end-station:*
  + Maximising the scientific return through measurements of the micro-biophysical impact of proton and light-ion beams requires that beam parameters (energy, dose, spot size) are measured for each shot in real time. The control system is required to ensure that the beam quality delivered to the sample is within the required tolerance. The principal risk to the successful integration of the beam, diagnostics and radiobiological-end-station is that the control system will take too long to respond to variations in the beam quality.

The in-vitro demonstrator facility will be constructed in a laboratory that will be provided by Imperial College London in the new White City Campus[[20]](#endnote-20). The exploitation of the radiobiology facility will therefore benefit from the wet-lab facilities that are available in the White City Campus[[21]](#endnote-21). The personnel required to provide the laboratory space and the services required for its operation will be provided by Imperial College London. Further, assurances have been received that we will be able to call on the mechanical, electrical and systems engineering expertise within the STFC Rutherford Appleton and Daresbury Laboratories during the preparation and construction of the laboratory space and the implementation of the radiobiology facility.

The work will be carried out by early-career researchers and graduate students in six work-packages, summarised in the paragraphs that follow. An internationally-recognised expert has been recruited, for each work package, to mentor and advise the early-career researchers in the execution of the programme.

### Work package 1: End-to-end simulation and performance validation

A full end-to-end simulation will be developed that integrates the partial simulations of the proton and ion source, the capture system, the beam transport, the ion-beam selection and the beam-delivery system. The simulation will include integration of the GATE[[22]](#endnote-22) simulation of the interaction of particle beams with tissue. This end-to-end simulation will then be used to optimise the critical parameters of the various components and to validate the performance of the full system. When the facility is in operation, the simulation will be developed such that it becomes a tool to interpret the micro-biophysical measurements. The updated simulation will become a valuable tool to enhance the precision of treatment planning software packages.

### Work package 2: Laser-driven particle source

The success of LARA to deliver proton and light-ion beams for radiobiology rests on the efficient commissioning of the laser-driven source. Therefore, priority will be given to the procurement, installation, and commissioning of the laser system and the associated particle-production target. The project plan foresees an extended period of commissioning and characterisation in which the particle flux produced by the laser will be fully characterised. The measured particle spectra will be used to inform the development of the end-to-end simulation.

### Work package 3: Ion-beam capture and initial focus

A revision of the design of the Gabor lens will take place in parallel to the preparation of the laser/target system. This will exploit the experience gained with the evaluation of the prototype lens that is under test at Imperial. The design-update, component-procurement programme and commissioning of the lens will be carried out in the first year of the project. The full project plan includes actions by which the risk associated with the Gabor lens noted above can be mitigated. By expediting the validation of the performance of the lens, risk-mitigation strategies can be employed such that the overall schedule for the delivery of the project will not be impacted. Once the performance of the Gabor-lens system has been validated, it will be installed and commissioned in the experimental hall.

### Work package 4: Beam transport and delivery

The beam transport and delivery system is composed of conventional components. The Wien filter, which is used to select the ion species, requires development for the relatively high-energy ion beam. The Wien-filter development programme will be carried out in collaboration with industry.

The principal challenge for the transport and delivery system is to transform the tiny beam spot created by the laser into a uniform dose over the sample that ranges from 1 mm to 30 mm in diameter. The requirement that the beam transport and delivery system be compact, having a total length of **?? m**, leads to the specification of optical parameters that vary by two orders of magnitude along the beam line.

The end-to-end simulation will be exploited to derive the mechanical and electromagnetic tolerances to which the beam-transport-and-delivery system must be built. Commissioning of the transport and delivery system will begin once the particle source and capture system are in place.

### Work package 5: Biological end-station

LARA will deliver a uniquely precise and well-characterised beam such that a pristine Bragg peak is delivered to the biological sample. For the end-station work-package, the principal challenge that must be met is therefore the integration of the beam-delivery system with the climate-controlled end-station and its associated diagnostic and dose-measurement systems such that the beam quality at the biological sample is not degraded. To achieve this, the end-to-end simulation will be used to complete a detailed specification of the end-station. This detailed design will include translation and rotation stages to allow multiple samples to be irradiated in one experimental session and include diagnostics, dosimetry, and imaging systems such that the dose delivered to each sample is recorded in real time in a central database. To expedite the commissioning of the system each component, and the full system, will be tested on the research beam line at MedAustron. The experience gained by the project team in these test exposures will be invaluable in the exploitation of the full system at Imperial.

### Work package 6: System integration, diagnostics, dosimetry and controls

An integrated control-and-monitoring system encompassing the accelerator, its diagnostics, and the diagnostics, dosimetry, climate-control, and imaging systems of the biological end-station, will maximise the efficiency at which the radiobiological experiments can be carried out. State-of-the art components will be used to form the integrated system. A commercial software framework (LabView[[23]](#endnote-23)) will be used. A fast-feedback system, required to ensure the safe operation of the facility and the real-time systems necessary to deliver the uniquely-defined beam to each sample, will be defined.

# The State of the Art

## 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 the rest if the patient.

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 iso-effective 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 (HBT) have led reviewers to conclude that, if HBT 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 cord 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.

## Radiobiology to enhance radiotherapy and to drive the evolution of clinical practice

**Lead author:** SG **To be updated.**

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[[24]](#endnote-24),[[25]](#endnote-25) 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.

### Accelerator systems for radiobiology and radiotherapy

**Lead author(s):** JPo,

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 a 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 with 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.

## Instrumentation, dosimetry, data handling, feedback and control

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

## 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[[26]](#endnote-26) 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 photon 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,[[27]](#endnote-27). Furthermore, studies reveal a differential regulation of signalling pathways in response to dose delivered using photon, light-ions and heavy ions[[28]](#endnote-28),[[29]](#endnote-29). 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.

# Objectives

## Overview

**Lead author:** KL

## Capability for radiobiology

(Including facility specification)

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

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.

## Laser-driven source and capture system

Laser-driven ions have been posited as a source for radiobiological studies for a number of years [refs]. The ion energies, energy spread, and shot-to-shot reproducibility of the produced flux has, until now, meant that they were unsuitable as a radiobiology laboratory source. 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], where 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 proposed system 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.

## Beam transport and beam delivery system

**Lead author(s):** JPa

The properties of the ion beam created by the laser-target interaction require several manipulations before it can be either used for radiobiological in-vitro studies or injected into post-accelerator. In this section objectives of the preliminary solution for the beam transport system are outlined with the focus to explain how to meet the goals of the facility for radiobiological in-vitro studies.

The ion beam at the target inherits its size from laser focused to a very small spot size, typically of the order of microns, however it has a very wide angular distribution. This is why even to capture a fraction of the beam a very strong focusing device is required in the form of either a strong solenoid or the Gabor Lens. The baseline solution for the system described in this proposal uses a Gabor Lens based capture, which technical details is described in the previous section. The role of the capture is to reduce the divergence of the beam, while maintaining manageable size of the beam. It is assumed the Gabor Lens is used to perform point-to-parallel beam transformation from the point-like source at the target, which creates relatively wide beam with a very large betatron function. This beam needs to be father matched using several quadrupoles to reduce the beam size, while keeping the divergence under control and a dedicated set of quadrupole lenses is used for this purpose. In addition to the manipulations in the transverse phase space, RF cavities can be placed downstream of the Gabor Lens in order to perform longitudinal phase space rotation to increase the beam intensity within the energy acceptance of the following particle selection section. Particle 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 being created simultaneously. While it seems ideal as a source for the facility utilising both of the particle species, there is a clear need to separate them for the irradiation studies. Firstly particles with different magnetic rigidities are being separated by introducing vertical bending magnet, which will generate beam dispersion and the correlation between beam energy and position. With the help of collimation required energy band can be chosen, however the sample can still contain different particle species or charge state, so following the collimation a Wien filter is introduce, which using a combination of electric and magnetic fields will allow to separate particles traveling with different speeds allowing for the final purification of the beam. Second vertical dipole will bring dispersion to zero as the correlation between beam position and energy is unwanted at the irradiation point and will bring the total deflection angle to 90 degrees turning the beam into vertical as required by the radiobiological studies. The final set of quadrupoles will set the final beam size for the in-vitro studies in the range of 1-cm 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 Fig. (X).

The in-vitro beam system will need to be equipped with several beam diagnostic devices to measure precisely beam position and 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 will 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.

# Methodology

## The project structure

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

Table 1 shows the project flowchart for this research proposal. The project plan can be subdivided into the following scientific work packages plus an organizational work package, namely:

1. Laser-driven particle source (WP-1)
2. Particle capture (WP-2)
3. Beam transport and delivery (WP-3)
4. End station for radiobiological research (WP-4)
5. System integration, diagnostics, dosimetry, data-handling, feedback and control (WP-5)
6. Project management (WP6)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Workpackages (WP)** | **Year 1** | | | | **Year 2** | | | | **Year 3** | | | |
|  | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| WP1: Laser-driven particle source |  |  |  |  |  |  |  |  |  |  |  |  |
| WP2: Particle capture |  |  |  |  |  |  |  |  |  |  |  |  |
| WP3: Beam transport and delivery |  |  |  |  |  |  |  |  |  |  |  |  |
| WP4: Endstation for radiobiological research |  |  | M1 |  |  | M2 |  |  | M3 |  |  | M4 |
| WP5 System integration |  |  |  |  |  |  |  |  |  |  |  |  |
| WP6: Project management |  |  |  |  |  |  |  |  |  |  |  |  |

b3 Project plan by work package

## Laser-driven particle source

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

The methodology for the laser-driven ion source can be characterised broadly into 3 phases; procurement, installation and commissioning, and operation.

### Procurement:

Upon successful award of funding, we envisage the purchase of a commercial laser system and associated source generation paraphernalia over the course of XXX months.

1. *The laser:* The laser system will have a peak power of at least 15 TW. The specific final laser system delivered would be dependent on negotiation with the relevant commercial partners and the final quoted costs during the tender process. Any delivered laser system will necessarily be a short pulse (~35fs) Ti:Sap based laser system capable of operating within strict tolerance margins, namely able to operate at 10Hz or greater, with 1% level energy stability and high laser contrast. The quoted 15 TW minimum peak power arises from comprehensive particle-in-cell simulations using the EPOCH code [REF], which has shown such a system is required to get achieve 8.9MeV protons, the stated maximum energy required for capture. Such a power is quoted as a minimum as the ideal system design would use higher powers to generate protons > 8.9MeV. This is desirable as the it allows mitigation against “failed” shots, in which the required peak ion energy is not achieved. The causes of such failed shots typically lie in fluctuations in laser energy and the prepared target uniformity. The variation in peak energy can be of the order of 10%, and so by operating in a regime away from these extremes, such risks are mitigated. Furthermore, 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].
2. *Ion production station:*

The ion production station will constitute a dedicated vacuum chamber system for delivery of the laser beam to target and subsequent acceleration. Vacuum transport lines are envisaged from the dedicated laser room (this is necessarily separate to minimise the hazards workers are exposed to and allows parallel working) to the interaction chamber. This will constitute a 1x1x1 metre vacuum chamber will be used for the interaction. This will house the tape target, all laser delivery and focussing optics, opto-mechanics and diagnostics as outlined in the costing section, required to generate a stable, reproducible proton/ion beam. Appropriate vacuum pumps/gauges/controls will also be required to reach vacuums of at least 10-6 mbar. Procurement of all such items will be from a number of different commercial partners.

### Installation and Commissioning

Laser installation and commissioning is envisaged to be completed by the commercial partner delivering the laser, with a final working system handed over to Imperial College operating with the pre-agreed parameters in line with those outlined above. Installation of the ion generation station will be conducted in parallel with the laser installation. This work is expected to take XXX 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 work and will be essential to fully describing the final deliverable beam properties. This optimisation stage will be to deliver the optimal proton/ion spectrum in terms of energy and flux, while still being in a stable regime of laser operation. The final beam parameters delivered will be defined by the beam transport and delivery system, and/or the radiobiological applications. We would envisage having a number of operating modes (laser and target type) to be able to deliver a range of proton and ion beams with varying energy profiles.

The laser-plasma group from Imperial College has extensive expertise in performing such installation and optimisation studies, on laser systems both at Imperial College and at national scale facilities worldwide. The commissioning phase is expected to be XXX months in duration.

### Operation

Operation of the system is envisaged to be through the delivery of a stable ion beam at energies up to 8.9MeV at 10Hz, as required. It is envisaged a dedicated operating scientist will be employed to run the system.

**Justify relative to state of the art including novel aspects, any high risk/high reward elements?**

**Highlight intermediate stages where results might require adjustment to the project planning?**

### Particle capture

**Lead author(s):** JPo

The particle capture project plan is covering the general tasks of physics and engineering 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 design drawings for lens production. The Task of the production of the lenses as well as their initial tests off the beam line will be dominating the work load in the second year of the project. In the third year will be used to gain experimental data of lens performance with beam with the goal to be ready for installation on the Project beam line and deliver first beam 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 at Imperial will be fundamental.

(Task description, duration, FTE A, ...)

Physics design of Gabor lenses, month 0-9, PhD student

Engineering design of lenses, month 0-12, 0.5 FTE engineering

Production of lenses, month13-18, 0.25 FTE engineering, 0.5 FTE workshop

Initial lens test, month 19-24, 0.25 FTE workshop, PhD student

Off beam line lens tests, month 25-36, 0.25 FTE workshop, PhD student

On beam line tests of capture system, month 37-48, 0.25 FTE workshop

### Milestones and Deliverables related to Capture

*Milestones*

*1 Physics design of capture section finished . 9 month*

*2 Engineering design of lenses finished. 12 month*

*3 Production of lenses finished 18 month*

*4 Initial lens tests performed 24 month*

*5 Beam tests of lens off project beam line finished 36 month*

*6 Capture system installed on beam line 40 month*

*7 Beam tests of capture system on beam line finished 48 month*

*Deliverables*

*1 Report on lens performance 12 month*

*2 Engineering drawings of the lenses 15 month*

*3 Lens hardware 18 month*

*4 Report on lens performance 40 month*

*5 Report on performance of capture system 54 month*

## Beam transport and delivery

**Lead author(s):** JPa

The beam transport system, which conceptual principles are described in a previous section can be straightforwardly implemented. The initial design is expected to evolve further and the beam optics calculations and beam dynamics simulations will serve to inform improvements. This work is expected to be carried out by the PG student within the CCAP supported by the RA both funded by this proposal. Working towards the implementation a care needs to be taken to ensure a proper mechanical support is provided for an inclined and vertically oriented parts of the beam line. This effort will be checked by the mechanical engineer in collaboration with the RA. She or he will also provide the detailed technical drawing of the system in close collaboration with the RA. The Gabor Lenses required by the capture system will be manufactured in house (see previous section), while all the magnets will be purchased externally, together with their power supplies. The magnet electrical system will be designed by the RA in communication with manufacturer and in consultation with RAL experts. Magnet system will be integrated with the central control system by another RA, supported by this proposal, who will also work on the beam diagnostics. The diagnostics will also be a central subject for another PG supported by this proposal. Vacuum system will also be designed by the RA in consultation with experts from RAL and its components will be purchased externally. The beam line assembly will be performed by the technical staff from Imperial supported by RAs and PG student. The beam commissioning will cared out over the duration of six months by two RAs supported by PG students and others. The radioprotection for the system is described in section b3.5.

### End-station for radiobiological research

**Lead author(s):** SG

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 cross correlate 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 comparison 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.

## System integration, diagnostics, dosimetry, data-handling, feedback and control

**Lead author(s):** DC, AK

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 a clinical 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 characterization 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 optimized 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.

#### 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.

#### 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.

#### 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.

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