Distributed, precise and personalised, particle-beam therapy for 2050

Laser-driven proton and ion sources are disruptive technologies that offer enormous potential to satisfy the anticipated growth in demand for particle-beam therapy (PBT). A laser-hybrid system, in which strong-focusing plasma lenses capture and transport the beam will allow clinicians to deliver PBT in a completely new regime, combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates (up to 10^9 Gy/s compared to conventional dose rates of order a Gy/s).

A substantial increase in demand for PBT is expected in high-income countries. In low- and middle-income countries an estimated 26.9 million life-years could be saved if radiotherapy capacity could be scaled up. The investment required to scale-up provision will generate substantial economic gains.

We propose to lay the technological foundations upon which the required scale-up in capacity can be delivered using a distributed network of precise, personalised, multi-species particle-beam therapy (PBT) centres. To do this we shall prove the critical new techniques, technologies, and systems by delivering a production system dedicated to the study of radiobiology.

Our research programme will:

- Prove the principle of the novel technologies required to transform the delivery of PBT for 2050;
- Create a production system in the UK dedicated to the systematic study of radiobiology; and
- Position the UK to become a world-leading industrial powerhouse for particle-beam therapy.

Grand Challenges Addressed

The technology-development programme on which we have embarked is designed to: **improve the efficacy of particle-beam therapy** by increasing our in-depth understanding of the biological effect of charged-particle beams; and **make 'best in class' treatments available to the many** by reducing the footprint future PBT systems such that a larger number of centres can be implemented across the country. We therefore seek to push back the ***frontiers of physical intervention*** by demonstrating in a production environment the technologies required to automate the delivery of multi-species PBT in a single system that can deliver ultra-high dose-rates with high precision. Our research will lay the foundation for the:

- Integration of imaging, real-time-treatment-planning, and fast feedback-and-control systems to automate the delivery of optimised, adaptive, multi-species particle-beam therapy; and for the
- Exploitation of the unique properties of the laser-driven source using a novel hybrid-accelerator technique to remove the instantaneous dose-rate limitation of today's cyclotron- or synchrotron-based PBT systems thereby allowing optimal delivery of PBT and the exploitation of new and novel techniques such as ultra-high dose-rate (FLASH) radiotherapy and the delivery of particle microbeams.

Research Vision and Ambition

Our ***vision*** is that the integration of the techniques that we shall develop in a novel system for radiobiology will prove the feasibility of the laser-driven hybrid-accelerator approach thereby laying the technological foundations of the programme required to transform the delivery of PBT for 2050.

Our ***ambition*** is to:

- Develop the techniques, technologies, and systems necessary to provide precise, automated, adaptive proton- and ion-beam therapy in a clinic-ready device that makes it cost-effective to meet the projected increase in demand using a distributed network of particle-beam therapy centres;
- Exploit the system approach to bring techniques and technologies into clinical practice as they mature;
- Execute a rolling programme of integration of prototypes of the various components in a production system dedicated to radiobiological research; and
- Engage with UK industry in the development of techniques, technologies, and prototype components and systems.

1 Need for a Large Grant

Particle-beam therapy transformed for 2050

The development of incremental improvements to systems that are already in production can be funded through a series of small grants. In contrast, we seek to redefine the way in which particle-beam therapy is delivered in 2050 and therefore require a large grant to allow us to initiate a holistic system-level R&D programme to maximise clinical benefit by creating a system in which:

- Movements of patient, organs-at-risk, and tumour are measured and used in conjunction with real-time dose-deposition imaging to adjust the dose delivered shot-by-shot;
- Novel computing techniques are used to allow real-time updates to the treatment plan to be made using algorithms based on detailed and precise measurements of the radiobiological impact of ion beams; and in which
- A laser-driven proton and ion source is combined with novel particle-capture, focusing, and acceleration techniques to deliver that combination of ion-species, energy, and dose-rate that maximises therapeutic effect while minimising dose to healthy tissue.

To maximise access requires that the footprint and cost of the integrated system is small enough to allow a distributed network of PBT centres to be implemented.

A multidisciplinary collaboration of clinical oncologists, medical and academic physicists, biologists, engineers, and industrialists is required to deliver the capabilities necessary to deliver such a transformative particle-beam therapy system. We have established such a collaboration.

Definition of scope of the present proposal

With the resources requested here we aim to:

Develop a deep understanding of the biological effects of PBT:

Treatment planning for proton and ion beams today is based on the 'relative biological effectiveness' (RBE) of particle beams. RBE is the ratio of the dose of a reference radiation (X-rays) to the dose that must be delivered using proton or ion beams to achieve the same biological effect. RBE is known to depend on a variety of factors including energy, dose, dose-rate, tissue type, and ion species. However, today a representative RBE value of 1.1 is used in proton-beam treatment-planning systems, while for carbon an RBE-weighted dose is used. A detailed, micro-biophysical understanding of proton-tissue interactions would allow enhanced treatment-planning systems to be developed. A systematic programme of radiobiology is required to underpin the development of a micro-biophysical understanding of proton- and ion-tissue interactions with precision sufficient for their biological effectiveness to be simulated with confidence.

Maximise the clinical efficacy of future PBT by creating a multi-ion system capable of delivering novel techniques such as FLASH:

We propose to develop a novel hybrid accelerator in which laser interactions create a large flux of protons or light ions which are captured in a series of strong-focusing plasma lenses, and formed into a beam. The hybrid approach harnesses the unique properties of the laser-driven source: delivery of a range of ion species (p to C^{6+}) from a single source in ultra-short pulses that each deliver an enormous instantaneous dose. We will create a uniquely flexible radiobiology system serving experiments over a range of beam momentum and dose rate. By removing the dose-rate limitation of conventional ion-beam sources, our systemn will allow detailed investigation of FLASH (ultra-high dose-rate) radiobiology.

Drive the future development of these ground-breaking technologies on the scientific, technological, and economic fronts: The choice of a novel system dedicated to the study of radiobiology as our principal deliverable:

- Will allow the key elements of a future clinical system to be proved in a production system;

- Demonstrate in operation that the large instantaneous dose created by a laser-driven source can be captured efficiently and delivered to an application-specific end-station; and
- Create a fully-integrated system dedicated to the elucidation of the proton- and ion-tissue interactions that underpin the the clinical efficacy of particle beam therapy.

The work proposed here will initiate a programme of development by which to transform PBT for 2050, create a production system that will enhance clinical practice in PBT now and in the future, and position the UK to become an industrial powerhouse for PBT.

Seminal five-year programme

Seven work-packages have been defined to deliver the programme. Ion-beam capture will be performed between 10 MeV and 15 MeV, the beam being transported to a biological end-station optimised for in-vitro studies. The completed system will be capable of upgrade through the addition of a novel fixed-field accelerator system to allow in-vivo experiments. Post acceleration is beyond the scope of this proposal.

1. *End-to-end simulation and performance validation:*
   The implementation of a full end-to-end simulation 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 G4DNA 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. The package will be used to support the experimental programme carried out in work-package 6. This will allow the simulation to be developed such that it becomes a tool to interpret the biophysical measurements. The updated simulation will also be developed to become a valuable tool to enhance the precision of treatment planning software packages. The software development work will be carried out in collaboration with the industrial partners.
2. *Laser-driven particle source:*
   The success of the hybrid-accelerator approach rests on the efficient operation of the laser-driven source. Priority will therefore be given to the development and evaluation of the laser/particle-production target system and the associated diagnostics using existing facilities. Procurement of the laser/target system will begin after a comprehensive design review at the end of year two. Installation and commissioning of the laser system and the associated particle-production target will be followed by commissioning. The measured particle spectra will be used to inform the development of the end-to-end simulation.
3. *Ion-beam capture and initial focus:*
   In parallel to the preparation of the laser/target system, a detailed re-evaluation of the design of the plasma lens that will be used to capture and focus ion flux will be carried out. This revision will exploit the experience gained in the operation of other similar plasma-lens prototypes. The manufacture of a prototype lens will be carried out in collaboration with the national laboratory and one of the industrial partners.
   The design-update, prototype construction, and performance evaluation will be carried out in the first two years of the project. The full project plan includes actions by which the risk associated with the plasma lens can be mitigated. The final design will be presented in the comprehensive design review at the end of year two. Following the review, lens manufacture will be carried out in collaboration with the industrial partner. The integration of the lens in the capture system will begin when the laser-driven particle source has been commissioned.
4. *Beam transport and delivery:*
   The beam transport and delivery system is composed of a combination of plasma lenses and conventional bending magnets. The combination of electrostatic focusing in the plasma lenses with the magnetic steering of the beam will be used to select the ion species. 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 at the sample that ranges from 1 mm to 30 mm in diameter. The requirement that the beam transport and delivery system be

compact leads to the specification of optical parameters that vary significantly along the beam line. The transport line consists of an 11 m horizontal section followed by a 90° bend that sends the beam vertically upwards into the biological end-station. Commissioning of the transport and delivery system will begin once the particle source and capture system are in place.

5. *Biological end-station:*
   The hybrid-accelerator approach will deliver a pristine Bragg peak to the biological sample. The integration of the beam-delivery system with the climate-controlled end-station and its associated diagnostic and dose-measurement systems must be performed such that beam quality at the biological sample is not degraded. The end-station will include translation and rotation stages to allow multiple samples to be irradiated in one experimental session and diagnostics, dosimetry and imaging systems to record the dose delivered to each sample in real time. Each component and the full system will be tested on existing facilities. The end-station will house all the equipment and facilities required for the culture and processing of both monolayer and 3D spheroid/organoid cell samples from a variety of different tumours and their relevant normal-cell controls. Initial experiments will focus on examining the impact of the beam on cell survival plus the levels and kinetics of DNA damage and repair in comparison to x-ray irradiation experiments conducted in parallel. New data will be compared to the substantial volume of data obtained in specific-cell models in response to protons and photons previously acquired by the project team.

6. *System integration, diagnostics, dosimetry and controls:*
   To maximise the efficiency with which the radiobiological experiments can be carried out by implementing an integrated control-and-monitoring system that encompasses the accelerator and its diagnostics as well as the biological end-station and its climate-control, diagnostics, dosimetry, and imaging systems. Novel computing techniques based on advanced computing devices will be developed to provide rapid response in real-time. The development of feature recognition as part of a programme of development of image-processing algorithms will be carried out in collaboration with the industrial partners.

7. *Co-creation of impact:*
   We will carry out a coordinated programme of staff development to ensure that the team required to take the programme forward is in place at the end of the project. 'Discipline-hopping' placements will be provided for each of the early career researchers employed in the programme. Post-docs and students will have the opportunity to work for extended periods alongside established personnel in the academic physics, medical physics, computing, and biology departments as well as with the national laboratory and industrial partner organisations. We believe this cross-institution training will be essential to the long-term sustainability of the programme.

   This work-package will also have responsibility for advising the leadership team of spin-out opportunities as they emerge. Guided by this input and discussion with the project team and other stakeholders, the flexibility to via resources between work packages will be exploited to seize spin-out opportunities and thereby to attract further resources into the programme.

Need for a large grant

To deliver a system that meets these specifications requires that advances in the fields of real-time imaging, image processing, radiobiology, simulation of tissue response to ionising radiation, fast-feedback and control, and proton- and ion-beam production and acceleration. The EPSRC "*Transformative Healthcare technologies 2050*" call is therefore the ideal vehicle by which to lay the technological foundations of the programme since coordinated investment in each of the underpinning capabilities is essential for the programme to achieve its goals. The ability to via resources between work-packages is essential to manage risk and deliver the programme and to allow individual technologies to be spun out as they mature.

2 National Importance

The UK is a world leader in the provision of particle beams for science and innovation. The UK's accelerator research and development community is vibrant and has an internally-recognised track record of seminal and leading contribution. In particular, the UK is a world leader in the laser-generation of particle beams and in the development of novel accelerator, diagnostic, imaging, and computing technologies.

Each of the two new NHS proton-therapy centres as well as the various private centres that are being developed employ state of the art accelerator technology provided by overseas suppliers. These centres will deliver proton-beam therapy to the UK community for the coming decade. A significant growth in demand for particle—proton- and ion-beam—therapy at home and overseas is widely anticipated. We propose to prove the principal in operation of the technologies required to deliver personalised, adaptive proton- and ion-beam therapy over a wide range of energy and dose rate in a single automated system. Our approach will position the UK to become a powerhouse in the delivery of advanced PBT systems that have a footprint small enough to allow a distributed model to be adopted to maximise access across the UK. As a result, our programme has the potential to generate the capability for the UK to become a supplier of advanced PBT equipment across the world.

3 Impact and Application Co-Creation

We have adopted a project structure that will allow the 'asynchronous exploitation' of the technologies that we shall develop. For example, the exploitation of novel high-throughput computing running novel feature-recognition algorithms to automate the adjustment of the position of the patient or target volume is likely to be an early opportunity to generate impact. The development and exploitation of such a system is aligned with the business plans of the industrial project partners.

The creation of a project team that has the diverse skill set and motivation to take the project forward to deliver the long-term goal is a priority. The sustainable development of the programme from proof of concept to spin out will require staff with a breadth of experience across the disciplines. The project leadership will implement a staff-development programme in which early career researchers, and more established staff, recruited into one of the partner organisations are seconded for significant periods to other members of the collaboration. As the project progresses, placements and/or staff exchanges will allow academic staff to work within the national laboratory or industry partner organisations. Staff from the clinical, national-laboratory and industrial partners will also have the opportunity to join the teams in the academic physics, biology, and computing departments. Resources to support the staff exchanges outlined above have been included in the costing prepared for this outline proposal and will be justified in the Pathways to Impact section of the full proposal.

Our programme seeks to transform PBT by driving a route to market for this disruptive approach to beam creation and delivery. We will deliver a prototype beamline for the exploitation of laser-driven ions for radiobiology—we will deliver the UK's first system dedicated solely to the study of this disruptive technology for this important healthcare application. Development of laser-driven sources for medical and industrial applications is now a global activity, with significant activity in Europe where new beamline facilities have recently been opened. This project is distinguished from other facilities in that it is focused on delivering a compact, scalable beamline that provides a prototype for eventual deployment in clinical environments. This project is also complimentary in that there are common technical challenges, providing clear motivation for collaboration. Our system can be used as an injector to a post-accelerator of conventional or novel design. This gives a near-term path to a true prototype of a clinical machine.

It is important to understand how our programme is viewed by patients and patient-input will help us frame our bids for continued support. Moreover, there is increasing emphasis on the involvement of patients early in the technology-development process. We therefore propose to engage with patients from the outset. This will also give us experience in presenting and explaining concepts in novel particle therapy to patients and carers, which will be of long-term value in itself.