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Transformative, personalised, precision particle-beam therapy for 2050

A. Research Vision and Ambition

A1. Vision

In the UK it is anticipated that 1 in 2 people will develop cancer[i]. The present incidence of 17 million new cases per year globally is predicted to increase to 27.5 million new cases per year by 2040[ii]. Radiotherapy (RT) is used in 50% of cancer patients and is already involved in 40% of cancer cures[iii]. The NHS long-term plan[iv] to increase the rate of diagnosis of cancer in the early, curative stage, implies an increasing need for therapeutic interventions including RT.

Photons are used most frequently to deliver external-beam RT. There is increasing emphasis on the exploitation of proton and ion beams in particle-beam therapy (PBT) for which the bulk of the beam energy is deposited in the Bragg peak that occurs as the beam comes to rest. This allows dose to be conformed to the tumour while sparing healthy tissue and organs at risk. The benefits of PBT are widely recognised. The NHS has invested £250M in particle- beam therapy (PBT)[v] and the Particle Therapy Co-Operative Group (PTCOG)[vi] currently lists 90 proton therapy facilities and 12 carbon-ion-therapy facilities[vii]. These facilities are located predominantly in high-income countries[viii]. Nearly 70% of cancer patients in low-and-middle-income countries globally do not have access to RT[iii].

The beam characteristics that can be exploited in PBT facilities today are restricted to low dose rates (<10 Gy/min), a small number of temporal schemes (a typical treatment is delivered in “fractions” of 2 Gy per day over several weeks) and a small number of spatial distributions (predominantly large beams delivering a homogeneous dose over several square centimetres). Clinical efficacy is dependent on the dose delivered which in turn is limited to minimise damage to the healthy tissues. The use of novel beams with strikingly different characteristics has led to exciting evidence of enhanced therapeutic benefit, e.g. therapy using very high dose per fraction[ix], very high dose rate (> 40 Gy/s, "FLASH")[x], and “mini-beam” (MBRT)[xi]. This evidence, together with developments in our understanding of personalised medicine based on the biology of individual tumours, now provides the impetus for a radical transformation of PBT.

Laser-driven proton and ion sources are disruptive technologies that offer enormous potential to satisfy the anticipated growth in demand for PBT by providing more flexible, compact and cost-effective high energy particle sources. We propose to develop a laser-hybrid system, in which novel strong-focusing electron-plasma (Gabor) lenses capture and focus the large flux of protons or ions created when a short pulse, high-power laser strikes a target, thereby delivering a wide variety of ion species in almost arbitrary time, spatial, and spectral structures. The laser-hybrid approach will also evade the instantaneous dose-rate limitation of current sources and deliver ultra-high dose rates of up to 10^9 Gy/s[xi] in pulses that can be as short as 10–40 ns. These short, intense pulses allow novel techniques such as proton- and ion-acoustic imaging to be used to determine the position of the Bragg peak for each pulse in real time. The capability of the system we propose cannot be delivered through incremental development of cyclotron-, synchrotron-, or linac-based PBT facilities.

Our vision is to radically transform the clinical practice of PBT by creating a fully automated, highly flexible system **to harness the unique properties of laser-driven ion beams to:**

- **Deliver particle-beam therapy in completely new regimens** by combining a variety of ion species from proton to carbon in a single treatment fraction exploiting ultra-high dose rates and novel spectral-, spatial- and spectral-fractionation schemes; and
- **Make “best in class” treatments available to the many** by reducing the cost of PBT per patient. The system we propose integrates patient, soft-tissue, and dose-deposition imaging with real-time treatment planning in an automatic system that triggers the delivery of dose tailored in real time to the individual patient. Our system will reduce the cost per patient by removing the requirement for a large gantry, thereby reducing the size (and therefore the cost) of a clinical PBT facility and increasing patient throughput by reducing the time spent in treatment.

We have created the multi-disciplinary collaboration of clinical oncologists, medical, particle, plasma, laser, ultrasound, and optical physicists, accelerator, computer, and instrumentation scientists, radiobiologists, industrialists, and patient representatives **required to realise our vision.**

A2. Ambition

Our ambition is to establish an entirely new technique for the automated delivery of personalised, precision, multi-ion PBT based on novel laser-hybrid accelerator technology **and**

to construct an experimental system to serve the measurement programme necessary to develop a fundamental understanding of tumour and normal tissue biology and biochemistry that underpins the clinical development.

The efficacy of proton and ion beams is characterised by their "relative biological effectiveness" (RBE) in comparison to reference photon beams. Recent studies have identified vital roles for specific proteins and mechanisms involved in the signalling and processing of DNA damage and repair as critical factors in the cellular response to protons[xi]. These results indicate that a systematic programme of measurement is vital for a full understanding of the processes that are induced by ionising radiation in tissue to be developed. Our roadmap to develop pre-clinical and full clinical systems therefore includes a proof-of-principle (PoP) laser-hybrid system[xi] for the biological assessment of multi-species PBT that will:

- *Improve the efficacy of PBT* by increasing our in-depth understanding of the biological effect of a wide range of charged-particle beams; and
- *Lay the foundations for the development of a PBT facility based on the laser-hybrid technique*.

With this Phase 1 proposal we seek the resources to:

- **Deliver an outline Conceptual Design Report for the PoP biological-assessment facility;**
- **Design a prototype proton- and ion-acoustic dose-deposition imaging system; and**
- **Carry out an initial healthcare-technology assessment study to quantify the benefits of the radical transformation of PBT we propose.**

Thus, we **aim to lay the foundations of a 5-year R&D programme to realise the PoP system in Phase 2** (Delivery Phase) of EPSRC's Transformative Healthcare Technologies programme.

A3. Grand challenges addressed

Developing Future Therapies: Supporting the development of novel therapies with technologies to enhance efficacy, minimise costs and reduce risk to patients.

The precisely controlled delivery of bespoke proton and ion beams has the potential to:

- Drive a step-change in the clinical practice of particle-beam therapy by creating the capability to deliver PBT in completely new regimens;
- Significantly reduce the number of treatment sessions and the treatment time, thus increasing throughput, thereby reducing cost.

Frontiers of Physical Intervention: Restoring function, and optimising surgery and other physical interventions to achieve high precision with minimal invasiveness.

Our approach is to deliver PBT with unprecedented precision through the integration of patient, soft-tissue, and dose-deposition imaging with treatment planning in a fully automated system thereby:

- Optimising the dose delivered fraction-by-fraction using multiple ion species delivered in spatial, temporal, and spectral distributions tailored precisely to the individual patient.

Optimising Treatment: Optimising care through effective diagnosis, patient-specific prediction and evidence-based intervention.

The study of the efficacy of ion beams, alone and in combination with systemic therapies, in a range of biological scenarios, will be central to the PoP programme and provide evidence for the initiation of clinical trials and the development of the clinical system. Our programme has the potential to:

- Optimise the precision of PBT through the use of detailed and precise time-resolved bio-physical data that is fully understood and well characterised;
- Deliver in real time precise, patient-specific treatment plans through the integration of patient, tissue and dose-deposition imaging in a fully automated system; and
- Create end-point-specific PBT treatment plans by exploiting the increasing knowledge of radio-genomics and systemic therapy interactions.

Transforming Community Health and Care: Using real-time information to support self-management of health and wellbeing, and to facilitate timely interventions.

Our system will allow patient involvement in the real-time optimisation of treatment because it will:

- Deliver automated PBT that compensates for movement of patient, target treatment volume and healthy tissue, determine the dose-deposition profile and update the treatment plan in real time to provide timely optimisation of treatment.

A4. Impact and benefits

As outlined above, our approach has the potential to reduce significantly the cost of PBT per patient. This will allow more inclusive access to the benefits of advanced multi-ion therapy and reduce patient

travel times, which is in line with the planned NHS net zero carbon footprint. The system we propose can be developed as part of a national strategy to meet the predicted increase in demand for PBT.

Today's PBT systems are provided by overseas suppliers. We seek to place UK industry at the forefront of the provision of fully automated laser-hybrid PBT facilities. Our multidisciplinary collaboration therefore includes a UK-based medical-equipment provider and UK companies specialising in high-throughput computing, algorithm optimisation, and highly advanced ultrasonics.

B. National Importance

We seek to establish an entirely new technique for the automated delivery of personalised, precision, multi-ion PBT. To do this we will bring together novel technologies, each developed for, or demonstrated in, unrelated fields. This programme carries significant technical risk. The high-risk approach is justified by the high level of reward and will place the UK at the forefront of the PBT field, establish UK industry as a key player in the delivery of novel clinical equipment, and allow significantly enhanced access to state-of-the-art PBT across the UK.

In addition to the long-term transformation of clinical practice in PBT, the national importance of our programme derives from the breadth of impact it will generate in the R&D and PoP phases:

Clinical: incremental deployment of automated on-the-couch patient-imaging and patient-positioning systems and development of fast, optimised treatment-planning software. Definitive *in vitro* and *in vivo* biological measurements that will be used to enhance the accuracy of treatment planning software in the short, medium, and long term.

Technological: Prototypes of novel accelerator technologies, novel real-time "proton-acoustic" dose-deposition imaging; automated robotic systems that can be developed for clinical application, optimised image-processing and treatment-planning systems, and a simulation of the full clinical facility to be used to optimise its efficacy and to inform its development, construction, and operation. Exploitation of the biological facility and incremental development of the novel technologies.

Industrial: The R&D prototypes and components of the PoP system will be developed and produced in partnership with the industrial members of the collaboration. Active involvement in the R&D and PoP activities will position UK industry to take a leading role in the implementation phase.

Scientific: Direct scientific impact will be generated in the fields of laser-driven acceleration, imaging, instrumentation, diagnostic-technology, and software-system development during the initial R&D phase. Scientific impact in the field of biology will be delivered during the PoP phase. Key technologies developed and proved in operation can be spun-out to accelerator-based infrastructure for science and innovation. Execution of the proposed programme will maintain and enhance the UK's internationally recognised position of leadership in the provision of intense, pulsed ion beams.

C. Application co-creation

C1. STFC matching funding for the Development Phase

We have presented a self-consistent conceptual design for the PoP laser-hybrid accelerator system which identifies the key technical risks presented by its development[xiv]. To lay the foundations for the 5-year R&D programme of the Delivery Phase (Phase 2), it is necessary to execute the first steps in the laser-hybrid accelerator risk-mitigation programme. This must be carried out in parallel to the development of the multi-ion biological assessment facility for which resources are requested in this Phase 1 proposal. The STFC has agreed to provide matching funding to support the essential risk-mitigation programme should this Phase 1 proposal be successful.

C2. Development Phase co-creation work programme

The Development Phase programme defined below is the first step in the long-term programme required to realise our vision of a radical transformation of clinical practice of PBT through an automated system based on the laser-hybrid acceleration technique. The collaboration places particular emphasis on the maximisation of impact during the 5-year R&D and the PoP phases of the overall programme. For example, the automation of the patient-positioning system is essential for us to deliver our long-term vision, has been identified as a desirable, incremental enhancement of clinical practice by collaborating clinical oncologists, is capable of being developed for deployment as a cost-effective addition to existing equipment, and is viewed as a priority by the collaborating medical-equipment provider. The co-creation of such a system based on optical sensors is already being discussed between medical and academic physicists, computer scientists, and the medical-equipment provider. The identification and delivery of a series of such impact co-creation opportunities will create an excellent, vibrant and sustainable, research environment and generate additional sources of revenue that can be invested to advance towards our long-term goal.

The Development Phase programme will be delivered in three work packages. The leadership of each work package has been chosen to emphasise the co-creation opportunities.

C2.1: Outline Conceptual Design Report for the PoP biological-assessment facility

The optimised technical specification of the novel instrumentation, diagnostics, dosimetry, automated robotic handling, and integrated automatic control systems required to maximise the impact of the PoP facility will be led by pre-clinical researchers (academic and lab-based biologists). Consultant medical physicists and clinical oncologists will join the pre-clinical researchers in the specification of imaging systems for use in the PoP *in-vitro* programme. The pre-clinical researchers will work with laboratory-based scientists and industrial partners to specify the preparation and automated processing requirements for *in-vitro* samples to be studied on site and to be transported for imaging in the laboratories of collaborating institutes. *In-vitro* studies will include large volume imaging in the 100 μm to mm range for the study of cellular processes in 5D (3D space, time and chemistry) at an atomic/molecular level. The results will be presented in an outline Conceptual Design Report which will define the Delivery Phase biological-assessment R&D programme.

Computer scientists will work with clinical oncologists, medical physicists, and academic and lab-based physicists and industrial partners to identify the computational resources required to support online image processing (including dose-deposition) and treatment optimisation. Requirements for simulation of the full clinical facility will also be assessed. The results will be presented in the Computing Development Plan and will define the Delivery Phase computing R&D programme.

Deliverables:

- Outline conceptual design report for the in-vitro and in-vivo biological end stations
- Computing Development Plan

C2.2: Work package 2: Proton- and ion-acoustic imaging

Knowledge of the position of the Bragg peak in relation to anatomy is essential. Quantification of the deposited dose distribution is required for our clinical-system vision, and to perform biological measurements in the PoP system. We will develop proton- and ion-acoustic (proton-acoustic) imaging to fulfil both needs.

Proton-acoustic imaging works in a similar way to emerging medical photoacoustic imaging. It can localise the Bragg peak with submillimetre accuracy, allowing a quantitative image of the dose to be reconstructed using the acoustic waves emitted when the energy deposited creates a temporally and spatially localised temperature (and hence pressure) rise. Our aim is in-vivo real-time 4D (space and time) proton-acoustic dose localisation and quantitative imaging with simultaneous multimodality ultrasound and motion tracking. Challenges will be met with fundamental ultrasound innovation. Good signal-to-noise ratio will be achieved by using proton/ion pulses about 100 times shorter than those used hitherto, adjusting the mini-/micro-beam size to generate acoustic fields that allow highly sensitive ultrasound transducers with novel configurations and beamforming to use different frequencies for different wave directions, acoustic wavefield averaging using massively parallel ultrasound processing, and compressed sensing. Novel full-wavefield speed of sound and attenuation imaging will provide patient-specific correction for accurate Bragg peak localisation and dose-image quantification.

Physicists expert in photoacoustic and ultrasound imaging will lead this work package in collaboration with medical physicists with expertise in dosimetry, and pre-clinical radiobiologists.

Deliverables:

- Design report defining proton-acoustic systems for biological research and for clinical use;
- Simulation of the performance of the proton-acoustic systems; and
- A full plan for the demonstration of the technique for execution in the Delivery Phase.

C2.3: Evaluation of the benefits of the initiative & optimisation of the R&D programme

Under the leadership of a senior clinical oncologist this work package will encompass:

- The prediction of the health-economic impact and benefit over and above the incremental development of existing facilities. The analysis will take into account likely healthcare costs and potential reductions in the cost of treating normal-tissue side effects and the magnitude of anticipated additional overall survival. The results will be compared with existing radiation and non-radiation therapies and with the predicted future patient numbers and tumour stages within the NHS long term plan. Estimates will be made in terms of quality adjusted life years (QUALYS) and will be assessed and compared with the UK NICE threshold.
- A scoping/horizon-scanning programme to understand the priority biological paradigms for

ultimate clinical translation. An iterative process involving clinicians, biologists and physical scientists will identify future needs, gaps and development potential. A roadmap for the experimental programme will be developed that will encompass international impact and the potential for collaborative networking.

Deliverables:

- Report quantifying the benefits of the automated, laser-hybrid accelerator PBT system;
- Report quantifying the benefits of the initial R&D and PoP phases;
- Report on initial optimisation of the impact (clinical and industrial) of the initial R&D programme;
- Report specifying future associated-training programmes to ensure the long-term continuing development of the project team; and
- Establishment of a communication and engagement programme to ensure the underpinning scientific programme is informed by emerging biological and clinical developments and that the biological, clinical and patient communities are actively engaged with the initiative.

C3. Development Phase stakeholder engagement development plan

Patient and public involvement is already part of our programme. PPI representatives, already embedded in the team, are engaged in the discussion of plans for the development of the initiative and are drafting a formal PPI Strategy for the collaboration. The Development Phase PPI programme will encompass engagement in public information activities; continued engagement in discussions regarding the technical choices which may affect patients; assisting in the creation of an "information hub" for the initiative; and development of clinician engagement activities.

Clinician engagement: The collaboration involves personnel directly involved in the management and delivery of radiotherapy services in NHS and UK academic departments. During the Development Phase we will engage with the key national professional and scientific bodies and PPI groups to solicit feedback on the development of our initiative.

Industrial engagement strategy: The long-term goal is to develop novel technologies which, through engagement and co-creation with industry, can be included in PBT solutions. The team has already engaged with a large, industry-leading medical device manufacturer to discuss their involvement.

We have also identified focussed areas of technology development which could be translated more quickly to industrial partners. Thus, we address both short-term and long-term industry engagement, which will be coordinated with the lead institution's technology transfer office.

C4. Governance framework

The collaboration leadership has extensive experience in the development of effective governance structures as well as project and risk management in a large complex project. Presently, the work of the collaboration is coordinated through a Steering Group (SG) in which all collaborating institutes and the interests of patients are represented. The collaboration's conceptual design of the PoP system was reviewed before publication by an international expert panel[xi]. The SG intends that further significant developments be subjected to a similar level of independent expert scrutiny.

The governance framework for the Delivery Phase will be developed in consultation with all stakeholders and include consideration of regulatory and ethics compliance. It is likely that the present SG will become the Institute Board, an Executive Board will co-ordinate the day-to-day work, and that strategic advice and oversight will be provided by an International Advisory Board.

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[xi] Citation withheld to satisfy the anonymity criterion that applies to this outline proposal.