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**