**Section a: Extended Synopsis of the scientific proposal (max. 5 pages, references do not count towards the page limits)**

1. Mission Need

Cancer is the second most common cause of death globally [1]. In 2018, 18.1 million new cancer cases were diagnosed, 9.6 million people died of cancer-related disease, and 43.8 million people were living with cancer [2,3]. It is estimated that 26.9 million life-years could be saved in low- and middle-income countries (LMIC) if radiotherapy capacity could be scaled up [4]. Novel techniques incorporated in facilities that are at once robust, automated, efficient, and cost-effective are required to deliver the required scale-up in provision.

Radiation therapy (RT), a cornerstone of cancer treatment, is used in over 50% of cancer patients [5]. The most frequently used types of radiotherapy employ photon or electron beams with MeV-scale energies. Proton and ion beams offer substantial advantages over X-rays because the bulk of the beam energy is deposited in the Bragg peak. This allows dose to be conformed to the tumour while sparing healthy tissue and organs at risk.

The benefits of proton and ion-beam therapy (PBT) are widely recognised. PBT today is routinely delivered in fractions of ~2 Gy per day over several weeks. Usually, each fraction is delivered at a low dose rate (<10 Gy/min) deposited uniformly over the target treatment volume. Exciting evidence of therapeutic benefit has recently been reported when dose is delivered at ultra-high dose-rate, >40 Gy/s (“FLASH” RT) [6, 7], or provided in multiple microbeams with diameter less than 1 mm distributed over a grid with inter-beam spacing of ~3 mm [8]. However, the radiobiological mechanisms by which the therapeutic benefit is generated are not properly understood.

I have established a multi-disciplinary consortium dedicated to the creation of the Laser-hybrid Accelerator for Radiobiological Applications (LhARA) [9]. LhARA is conceived as the new, highly flexible, source of radiation that is required to explore the vast “terra incognita” of the mechanisms by which the biological response to ionising radiation is determined by the physical characteristics of the beam [10]. The technologies demonstrated in LhARA have the potential to be developed to allow PBT to be delivered in completely new regimens. Through the delivery of LhARA the consortium seeks to:

* Create the capability to deliver particle-beam therapy in completely new regimes by combining a variety of ion species in a single treatment fraction and exploiting ultra-high dose rates, multiple ion species, and novel spectral and spatial-fractionation schemes; and
* Make “best in class” treatments available to the many by demonstrating in operation a system that incorporates dose-deposition imaging in a fast feedback-and-control system thereby reducing the requirement for an extensive beam-delivery system and large gantry.

LhARA will exploit a laser to create a large flux of protons or light ions which are captured and formed into a beam by strong-focusing plasma lenses. The laser-driven source allows protons and ions to be captured at energies significantly above the proton- and ion-capture energies that pertain in conventional facilities, thereby evading the current space-charge limit on the instantaneous dose rate that can be delivered [10]. The plasma (Gabor) lenses provide the same focusing strength as high-field solenoids at a fraction of the cost.

The success of the LhARA initiative rests on the efficient capture of the laser-driven ion flux. While the production of protons and light ions using a high-power laser has been demonstrated [11] and a number of plasma-lens schemes are under development [12], the integration of a laser-driven source with a strong focussing plasma lens has not been attempted to date. Therefore, with this proposal I seek the resources to:

* Prove the principle of laser-driven injection of a large instantaneous flux of high-energy protons and light-ions into a novel strong-focusing plasma lens;
* Demonstrate the efficient capture and transport of the laser-created ion beam; and
* Carry out initial in-vitro measurements of the radiobiological impact of proton beams using the unique proton beam that will be produced.

The programme I propose will prove in operation the basis of the laser-hybrid technique and lay the foundations for the development of laser-hybrid accelerator systems capable of serving the particle-beam therapy facilities of the future. Furthermore, by evading the current space-charge limit, I will create a new proton- and ion-beam source with wide application in future high-power accelerator facilities.

Cancer is the second most common cause of death globally, accounting for 9.6 million deaths in 2018. It is estimated that radiotherapy is indicated in half of all cancer patients. However, nearly 70% of cancer patients worldwide do not have access to radiotherapy. Analysis of the trends in cancer diagnosis and treatment indicates that, by 2035, 26·9 million life-years in low- and middle-income countries could be saved if the radiotherapy capacity could be scaled up. Novel techniques such as those proposed here are required if the necessary scale-up in provision is to be delivered.

Today's stereotactic X-ray beam radiotherapy (SBRT) achieves doses and local tumour-control rates well above those that have been achieved in the past. Recent advances in four-dimensional computed tomography (4DCT), intensity modulated radiotherapy (IMRT) and other state-of-the-art photon technologies allow the X-ray dose to be concentrated over the tumour volume. The dose delivered by X-rays falls exponentially with depth. Therefore, the location of primary tumours in relation to healthy organs such as heart, lungs, oesophagus, and spine implies a fundamental limit on the X-ray-dose intensities that may be delivered.

Proton and ion beams lose the bulk of their energy as they come to rest. The distribution of energy deposition therefore has a pronounced ‘Bragg peak’ at the maximum range. Proton and ion beams overcome the fundamental limitation of X-ray therapy because, 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 Bragg peak occurs at the maximum range of the beam, treatment can be precisely conformed to the tumour volume.

The benefits of proton and ion-beam therapy (PBT) are widely recognised. Today, PBT is routinely delivered in fractions of ~2 Gy per day over several weeks; each fraction being delivered at a rate of approximately 10 Gy/minute deposited uniformly over the target treatment volume. Exciting evidence of therapeutic benefit has recently been reported when dose is delivered at ultra-high dose-rate, > 40 Gy/s (“FLASH” RT), or provided in multiple micro-beams with diameter less than 1 mm distributed over a grid with inter-beam spacing of ~3 mm. However, the radiobiological mechanisms by which the therapeutic benefit is generated are not entirely understood. 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.

To increase the availability of particle-beam therapy requires that the cost and complexity of the facility be reduced. To drive down the cost of particle-beam-therapy facilities requires that novel accelerator technologies be developed. The deployment of such technologies will make it possible to scale-up the provision of particle-beam therapy thereby allowing a greater fraction of the European and global population to benefit. The instantaneous dose that can be delivered today is limited at the proton- and ion-source which produces particles with energies of tens of keV/u. At such low energies, the Coulomb repulsion between the particles that make up the beam limits the beam-current that can be captured and accelerated. I propose to overcome this limitation by exploiting the laser-driven particle-production technology developed at Imperial College London to inject proton and light-ions at high-energy (up to 10 MeV) into a strong-focusing particle-capture system based on a plasma (Gabor) lens. Taking this approach makes it possible to deliver multiple ion species from a single source and to overcome the beam-intensity limitations that arise from the Coulomb repulsion of the ions in the beam as they emerge from the low-energy source.

The increasing emphasis on proton- and ion-beam therapy justifies an energetic programme of measurement that is best carried out in a purpose-built facility that is 100% dedicated to research. The hybrid approach I propose will combine the benefits of the laser-driven source with conventional beam transport and delivery. This will allow the biological effect of a range of ion species to be studied over a wide range of dose rates in a single dedicated facility.

References

Arguments not used:

Local cancer control is of great importance to quality of life and overall survival. There is powerful evidence that the investment required to scale-up the provision of radiotherapy would generate substantial economic gains as well as reduce the global cancer burden.