High dose delivery in radiobiology experiments employing laser-driven protons

Contact: m.borghesi@qub.ac.uk

P. Martin, O. Cavanagh, P. Chaudhary, C. Fegan, K.Prise
A. McCay, J. Morrow, S. Kar, M. Borghesi
Centre for Light-Matter Interactions,
School of Mathematics and Physics,
Queen's University Belfast,
Belfast, BT7 1NN, UK

Patrick G. Johnston Centre for Cancer
Research, Queen's University Belfast,
Belfast BT9 7AE, UK

H. Ahmed
Central Laser Facility,
STFC Rutherford Appleton Laboratory,
Didcot, Oxfordshire, OX11 0QX, UK

Abstract

High energy protons accelerated by the VULCAN laser have been used, in several campaigns, to irradiate cells and investigate the biological effects of irradiations at ultra-high dose rates. The use of a novel helical coil target design has enabled the production of highly collimated proton bunches, greatly increasing the dose delivered to the cells in the relevant energy ranges. We discuss here the irradiation of cell samples using both the standard flat foil and helical coil target configurations, with the latter delivering very high doses to the cells of up to 70 Gy in a single irradiation. This large dose range enables clinically relevant studies of the effects of ultra-high dose rate on various cell types, in studies of potential relevance to the FLASH mechanism of radiotherapy and future approaches to cancer treatment.

1 Introduction

Soon after the discovery of laser-driven ion acceleration, particularly the mechanism of target normal sheath acceleration (TNSA) [1], the potential use of laser driven protons for biomedical applications, and in particular cancer therapy, was proposed and considered Bulanov2002240. In particular, the dose rate deliverable by laser-driven proton bursts is many orders of magnitude greater than what is feasible with conventionally accelerated protons, on the order of 10^9–10^{10} Gy/s [2].

Experiments in radiobiology employing laser-driven protons have been initiated by several groups worldwide over the past 10-15 years (e.g. see [2] and references within), with the aim of identifying any peculiar features in the cellular response associated with these extreme irradiation regimes. Experiments by our group on the VULCAN [3] and GEMINI [4, 5] laser systems have focussed on the use of single ion pulses to obtain the highest dose rates, as opposite to other approaches employing multi-pulse irradiation to build up the dose delivered to the samples (e.g. [6]). In previous VULCAN experiments, we have employed a compact set-up

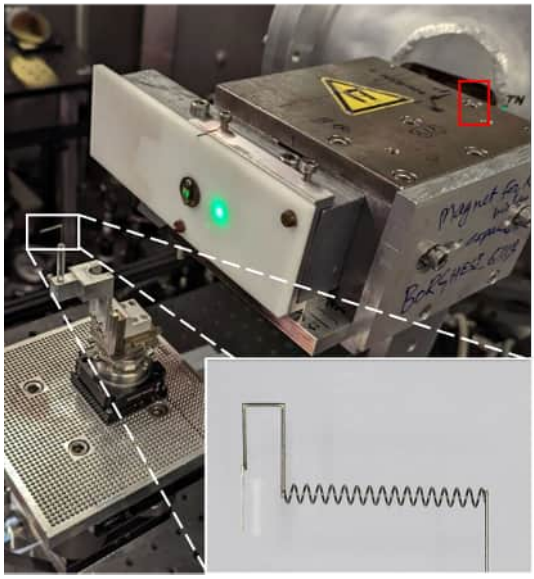

Figure 1: An image of the experimental setup for cell irradiation. A pinhole 8 cm from the target (indicated by the white box) leads into a dipole magnet, separating protons by their energy and leading to a kapton window, behind which the cells are placed. The red box highlights the cell plane which 35 MeV protons were incident upon. The inset shows a side view of a typical helical coil target used in the campaign, designed to produce a high flux of protons at around 35 MeV.

employing a large dipole-magnet to disperse the protons according to their energy, which has typically resulted in doses per shot of the order of a few Gys [3]. Depending on the biological assay and cell-type employed, however, higher doses, of order 10 Gy and above, are required for a complete assessment. This dose range is also of relevance to FLASH studies, where not only the dose rate but also the dose per pulse is an important parameter [7]. A method for increasing proton flux significantly enough to enable accessing this regime is through the use of helical coil (HC) targets, as was first demonstrated by Kar

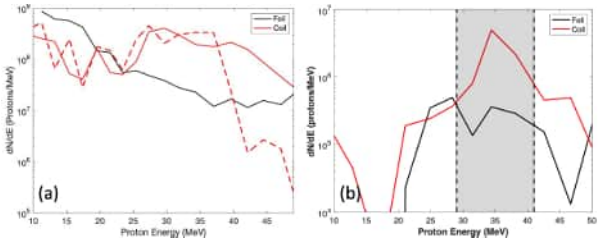

Figure 2: The proton spectrum from RCF for flat foils (black) and helical coils (red), with the RCF stack placed ***(a)*** *before the magnet, ∼8cm from the interaction point, and* ***(b)*** *after the magnet, at the cell plane. The dashed red line is a second HC shot, to demonstrate consistent flux around the 35 MeV point. The grey area indicates the approximate energy range which the cells were irradiated by.*

et al. [8]. The HC target post-accelerates and focusses the proton beam into a highly collimated, narrowband bunch, thereby increasing the flux in the energy range of interest by over an order of magnitude.

2 Experimental Results

The experiment was conducted on the petawatt arm of the VULCAN laser system. Here, pulses of 750 fs duration full width at half maximum (FWHM) and energies in the range of 250-300 J, were incident on gold flat foil targets, 15 μm in thickness. The laser was focussed to a spot ∼5 μm in diameter (FWHM), resulting in peak on-target intensities in the range $3 - 5 \times 10^{20}$ W/cm^2. For the production of the highest doses possible, these foils were attached to helical coils at their rear side. These coils were designed with diameters and pitches to produce bunches of tightly focussed protons, with spectral peaks centred around 35 MeV. After acceleration from the targets, the protons would enter a 12.5 cm, 1 T magnet, which disperses the protons by their energy, and leading on to a kapton window behind which the cells were positioned precisely at the point where 35 MeV protons were incident. An image of the experimental setup is shown in Figure 1 .

The white box highlights the target position, and the inset shows a side image of a typical HC target shot in the campaign. The laser, incident from the left, generates protons via interaction with the target, which then pass into the magnetic spectrometer, placed 8 cm downstream. The red box highlighted in the figure shows the position on the kapton window of the 35 MeV protons after dispersion, and therefore the point at which the cells to be irradiated were placed.

Before cells could be irradiated, a full spectral characterisation of the protons produced by the foils and the HC's, both before the magnet and at the cell plane, was performed using stacks of radiochromic film (RCF). Typical spectra are shown in Figure 2. As can be seen for the proton spectra both before and after magnet dispersion, the flux is increased by roughly an order of magnitude when using HC targets, as compared to flat foils. This is in line with what is expected and has been observed previously on VULCAN [9].

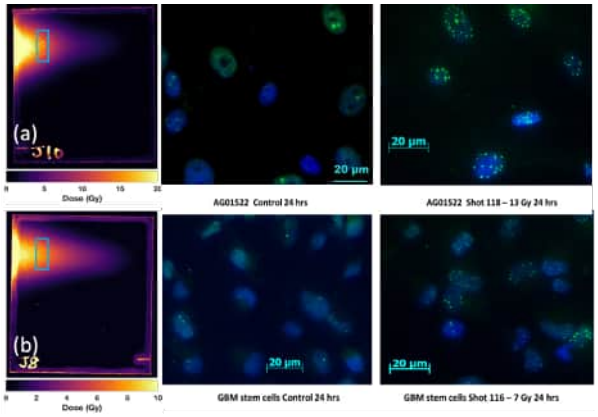

Figure 3: Laser driven proton induced DNA double strand break damage 24 hours after irradiation in ***(a)*** *normal human skin fibroblasts (AG01522) and* ***(b)*** *patient derived glioblastoma stem cells (E2) detected using 53BP1 foci formation through immunofluorescence staining. Cells were fixed 24 hours after irradiation. Each green dot represents a DNA double strand break and blue staining shows cellular nucleus. Dose-converted RCF for each shot is shown on the far left, the cyan boxes indicate approximate position of cells with respect to the RCF.*

Typical results of cell irradiation are shown in Figure 3 below. The DNA double strand breaks (visualized as fluorescence foci in the images) are shown for two different cell lines, normal human skin fibroblasts and glioblastoma stem cells. The RCF associated with each respective shot is also shown on the left, with the cyan area highlighting the approximate position of the cells. Doses of approximately 13 Gy and 7 Gy were recorded for these two shots, respectively. However, the HC tar-

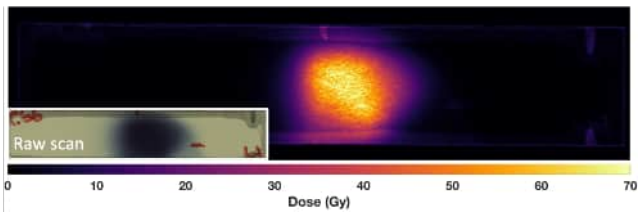

Figure 4: Dose-converted RCF layer for a shot on cells from a HC target, showing doses in the cell plane in the region of 60–70 Gy. The inset shows the raw scanned image, before dose conversion.

gets also demonstrated the capability to produce doses significantly greater, in the region of tens of Gy. Figure 4 below shows the RCF from one such shot. The average dose in the target region of the cells was between 60-70 Gy. While this is higher than typically used in radiobiology experiment, it points to the possibility of delivering doses in the 10s of Gy per irradiation, which would be of relevance to in-vivo irradiations in the context of FLASH radiotherapy studies [10].

3 Conclusion

The laser-driven acceleration of protons at high doses and ultra-high dose rates has been experimentally shown with the use of helical coil targets to maximise dose incident on the cells. A wide range of doses up to 70 Gy has been produced and used to irradiate cells, which will enable a better understanding of novel FLASH effect method of cancer treatment.

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