Pre-clinical evaluation of lethal and sub-lethal DNA damage in AG01522 and HUVEC cells by ultra-short pulse and ultra-high dose rate laser accelerated protons

C. Maiorino\textsuperscript{1}, P. Chaudhary\textsuperscript{1}, D. Doria\textsuperscript{2}, L. Romagnani\textsuperscript{3}, K. Polin\textsuperscript{2}, L. Manti\textsuperscript{4}, F.M. Perozziello\textsuperscript{4}, K. Prise\textsuperscript{1}, M. Borghesi\textsuperscript{2}

\textsuperscript{1} Centre for Cancer Research and Cell Biology, Queen’s University Belfast BT7 1NN, Belfast, UK
\textsuperscript{2} Centre for Plasma Physics (CPP), Queen’s University Belfast, BT7 1NN, Belfast, UK
\textsuperscript{3} LULI, Ecole Polytechnique, CNRS, CEA, UPMC; 91128 Palaiseau, France
\textsuperscript{4} School of Physics, University of Naples “Federico II”, 80126 Naples, Italy

Particle therapy has been cited as an effective treatment modality compared to photons and electrons based therapies for solid tumors located in close proximity to critical organs, such as spinal cord, brain and heart. Numerous studies have demonstrated the feasibility of using high LET particles in tumor cells; however, the very high installation and operational costs limit the outreach of particle therapy. The idea of future facilities based on laser-driven ion accelerators has been proposed as a way of reducing complexity and cost. Due to the ultrashort duration ($10^{-12}$ s) of these beams and their consequent ultrahigh dose rates (up to $10^9$-$10^{10}$ Gy/s), these beams can deliver lethal DNA damaging dose which tumor cells with unstable genome fail to repair, while normal cells are able to repair the same damage.

Our project aims to optimize and validate the dose distribution of laser-driven proton beams at high energies (~10 MeV), and to study the effectiveness of these beams in cell lethal and sub-lethal damage induction. We investigated the effects of the laser driven protons on DNA DSB damage, cell survival and stress induced pre-mature senescence (SIPS) in human skin fibroblasts (AG01522) and endothelial cells (HUVEC) in several laser facilities based in the UK and France.

We observed a close similarity between the laser accelerated and conventional clinical proton beams induced DNA DSB damage and SIPS and their enhanced effectiveness compared to low LET radiation (225 kVp X-rays). An increased cell killing was observed with laser accelerated protons compared to X-rays for the delivered doses above 1Gy. Our results can be used as an input to other tumor cell killing models for further optimization of the laser driven proton therapy in conjunction with DNA repair inhibitors and radioresistant tumors.