ITRF Kick-off Meeting: Current/Future Radiobiology Research

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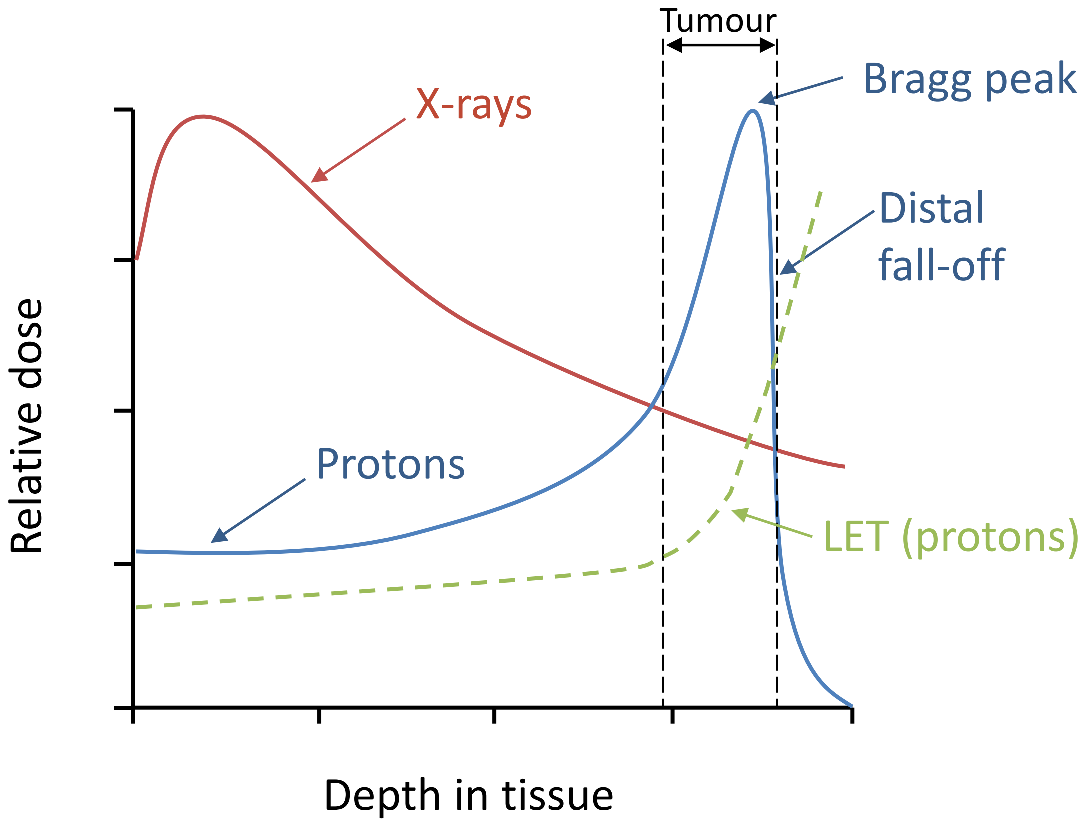
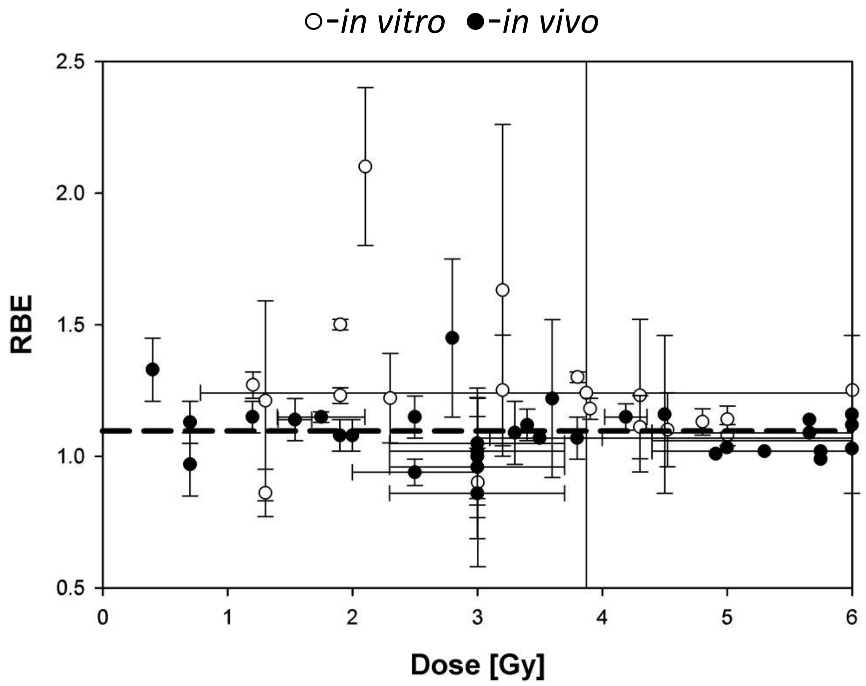
The advantages but also biological uncertainties following proton beam therapy





Taken from Paganetti and van Luijk (2013) Sem Rad Oncol

- Further research exploiting the biological impact of PBT is vital for establishing biological effectiveness (RBE) and optimal clinical treatment for tumours.

Vitti and Parsons (2019) ***Cancers***

Current projects investigating the radiobiological impact of protons and high-LET particles

- Realizing the radiobiological impact of protons and high-LET particles in head and neck cancer and glioblastoma models (NIH).
- New insights into the cellular responses to complex DNA damage induced by proton beam therapy (MRC).
- Improving the biological response of proton beam therapy in head and neck cancer (NWCR).

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust

MRC Medical Research Council

north west cancer research
Putting our region's cancer needs first

R01CA256854-01
NIH National Institutes of Health
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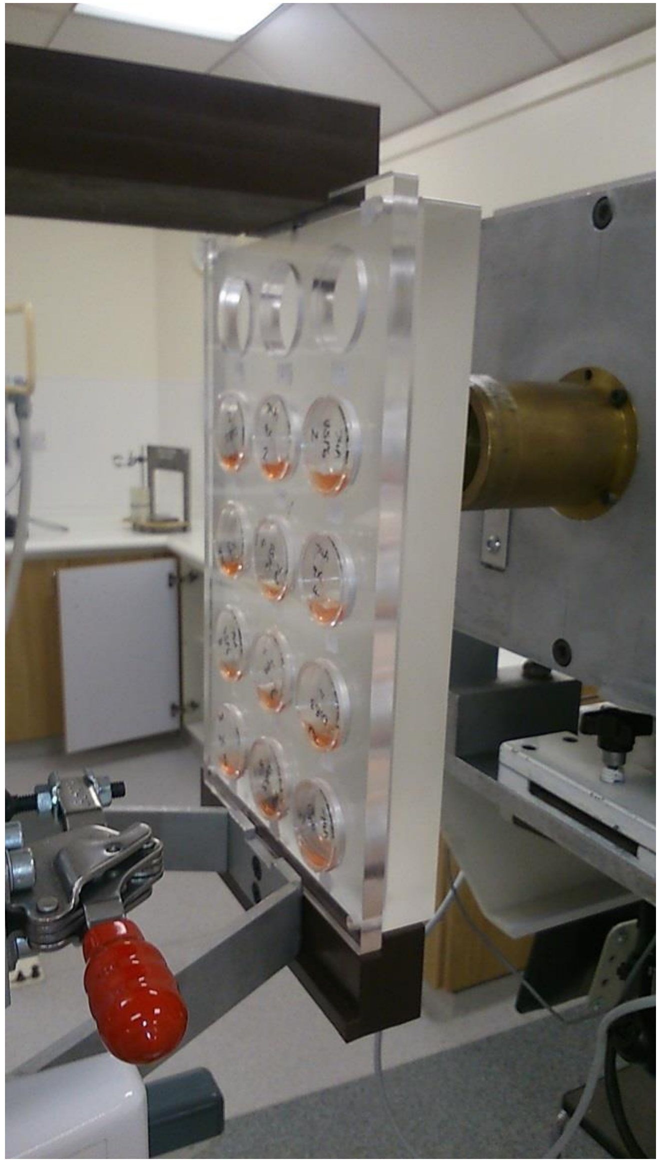
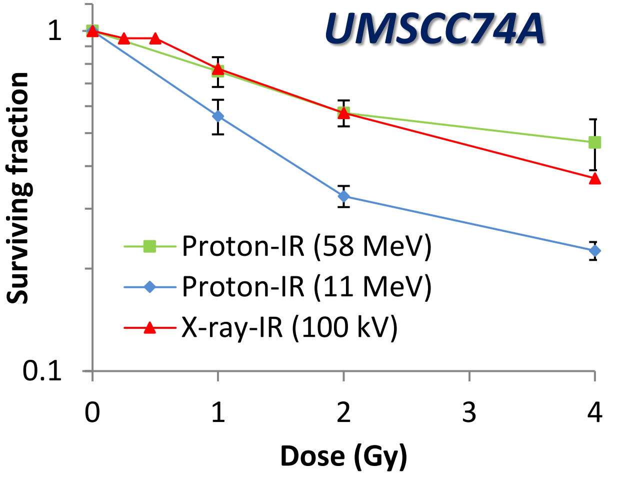
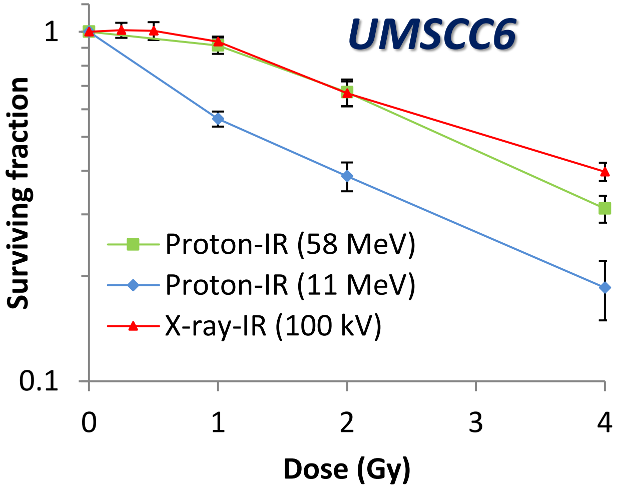
Proton beam and radiobiology facilities at the Clatterbridge Cancer Centre (CCC)



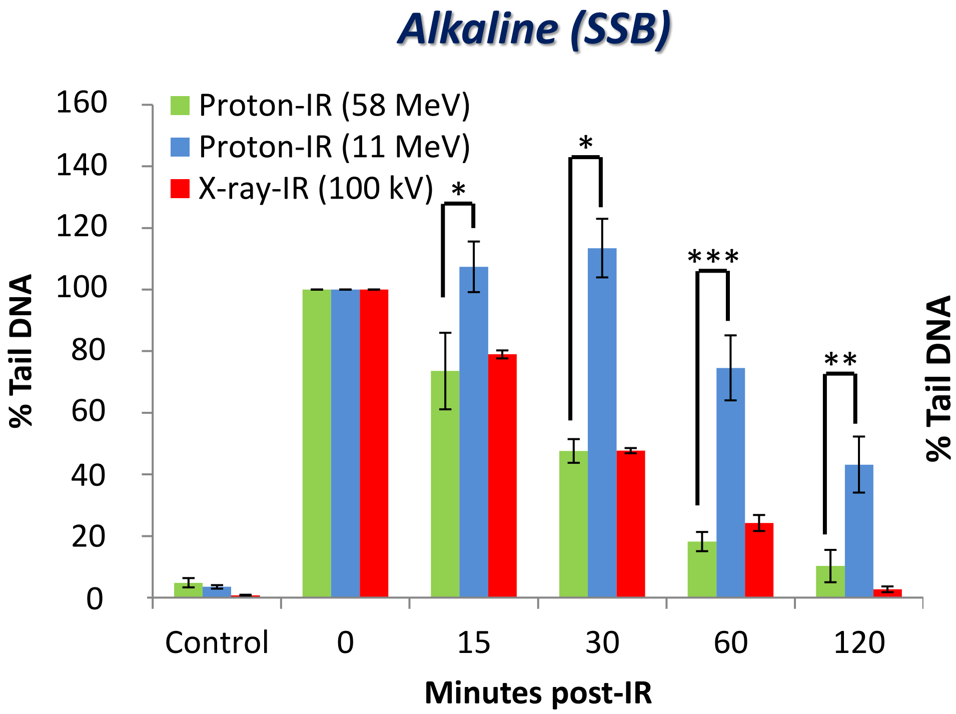
"Relatively" high-LET protons cause a decrease in HNSCC cell survival due to CDD formation compared to low-LET protons



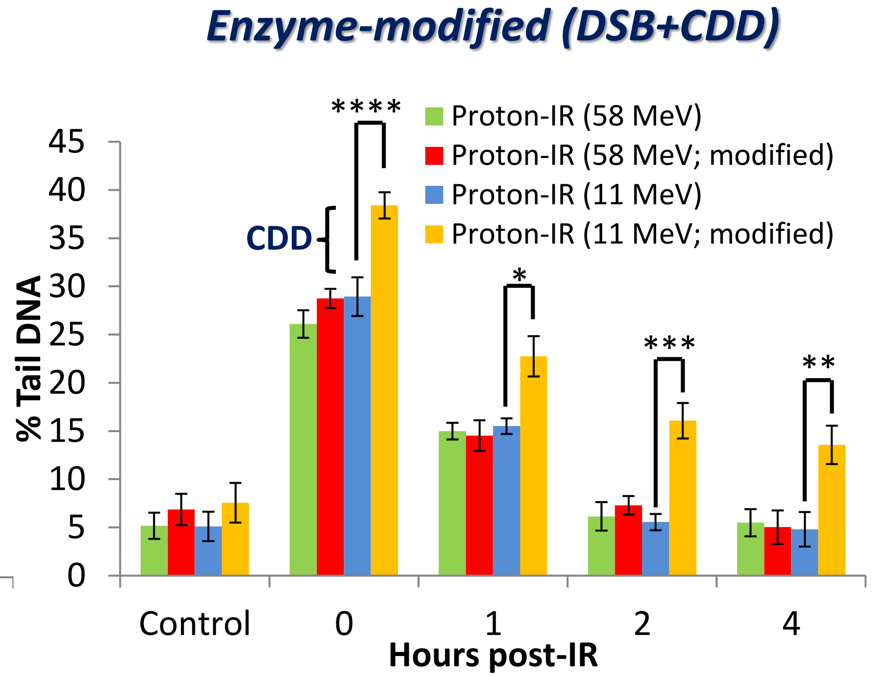
SF2, $p<0.02$; RBE=1.7



SF2, $p<0.01$; RBE=1.9



*$p<0.005$, **$p<0.002$, ***$p<0.001$

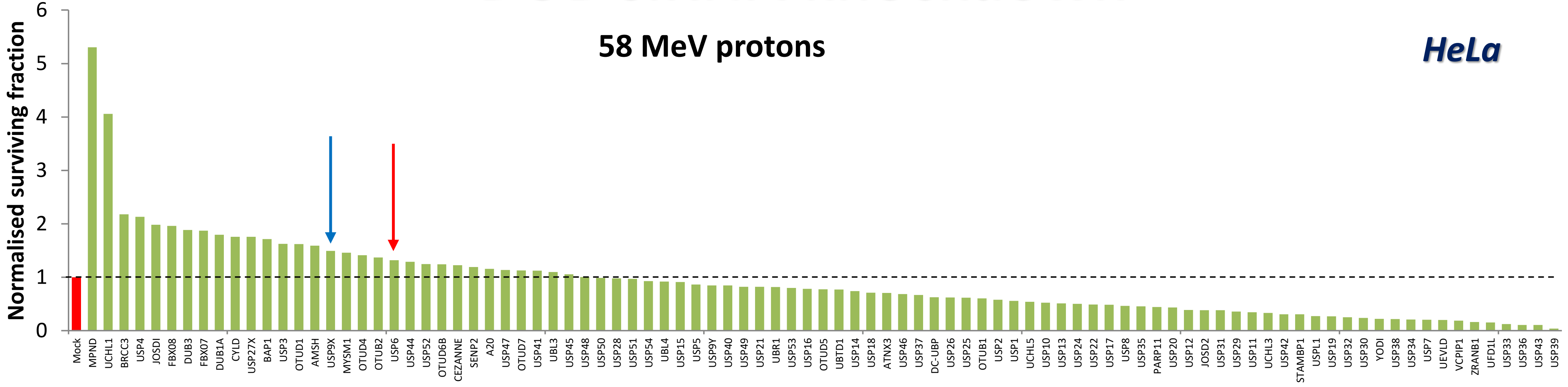


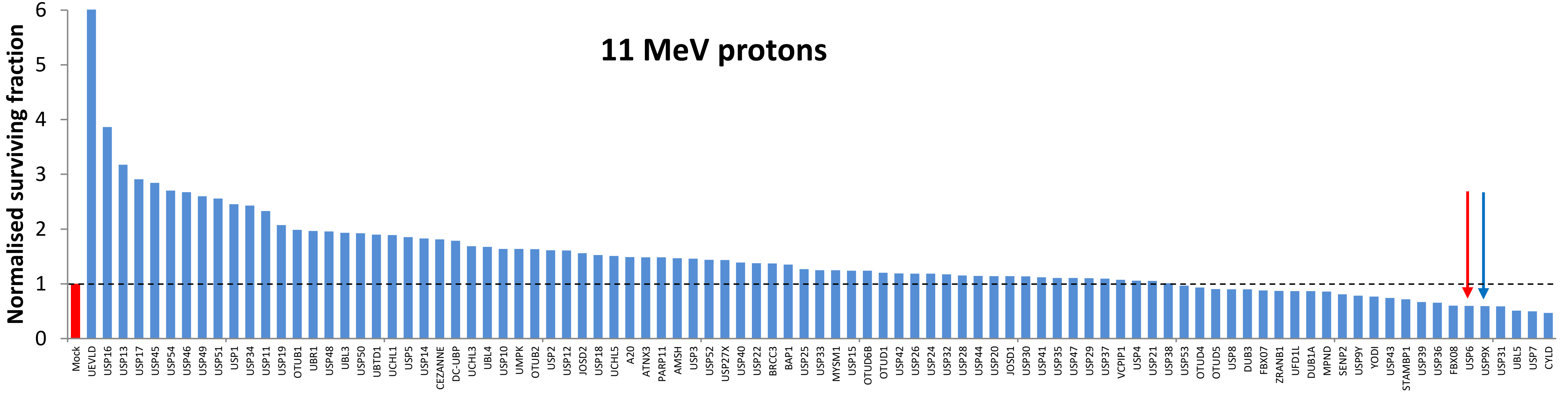
*$p<0.02$, **$p<0.01$, ***$p<0.005$, ****$p<0.001$

58 MeV (1 keV/µm); 11 MeV (12 keV/µm)

Carter *et al.*, (2018) *Int J Rad Oncol Biol Phys*
Fabbrizi *et al.*, (2021) *Methods Protoc*

Modulation of proton-induced cellular sensitivity following DUB siRNA knockdown



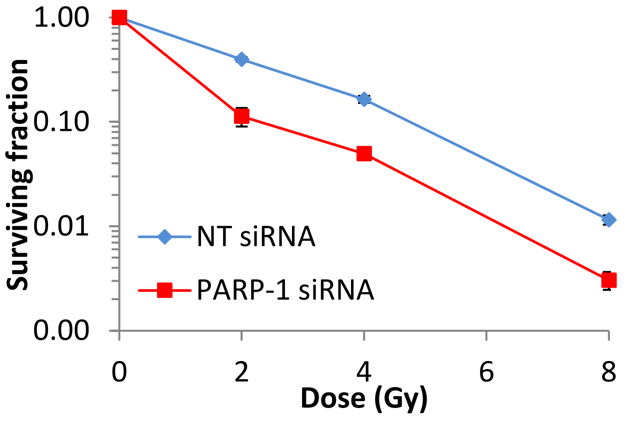


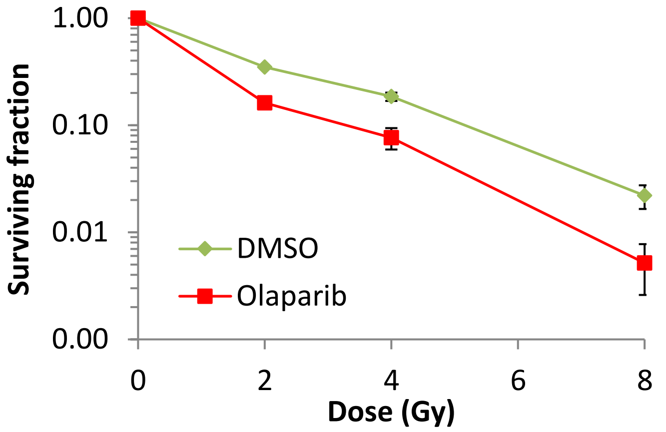
Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*
Nickson, Fabbrizi *et al.*, (2021) *Front Oncol*

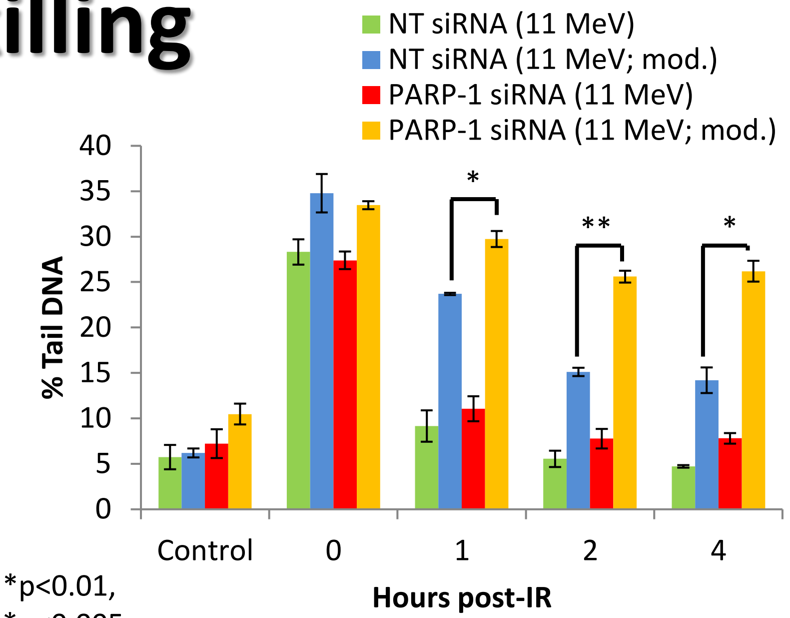
Targeting PARP-1 synergies with relatively high-LET protons in promoting cancer cell killing

HeLa

11 MeV

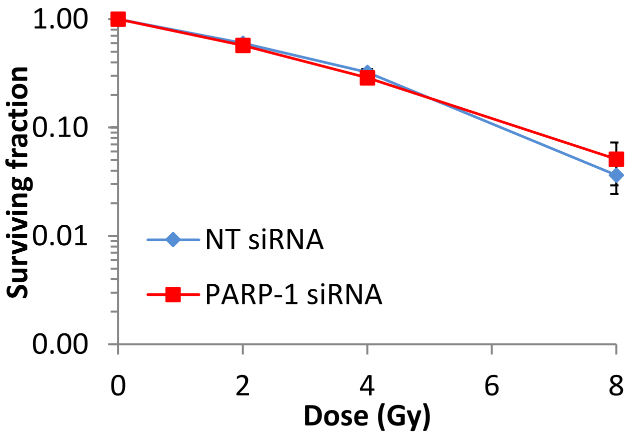


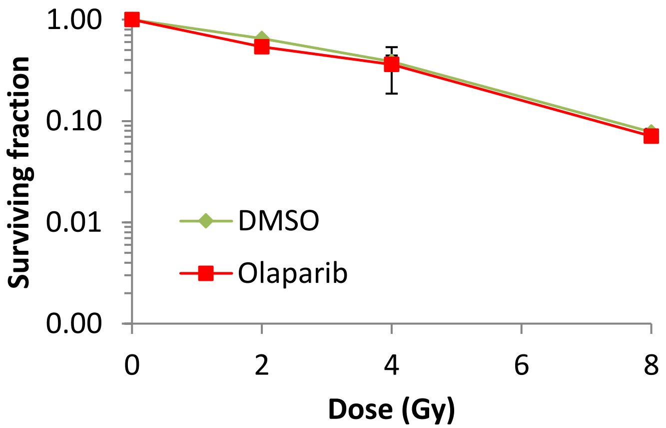


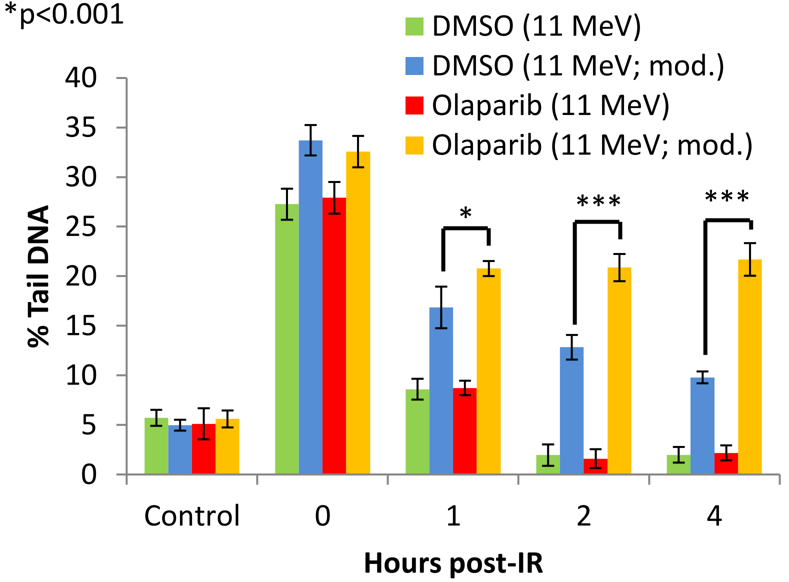


*p<0.01,
**p<0.005,
***p<0.001

58 MeV

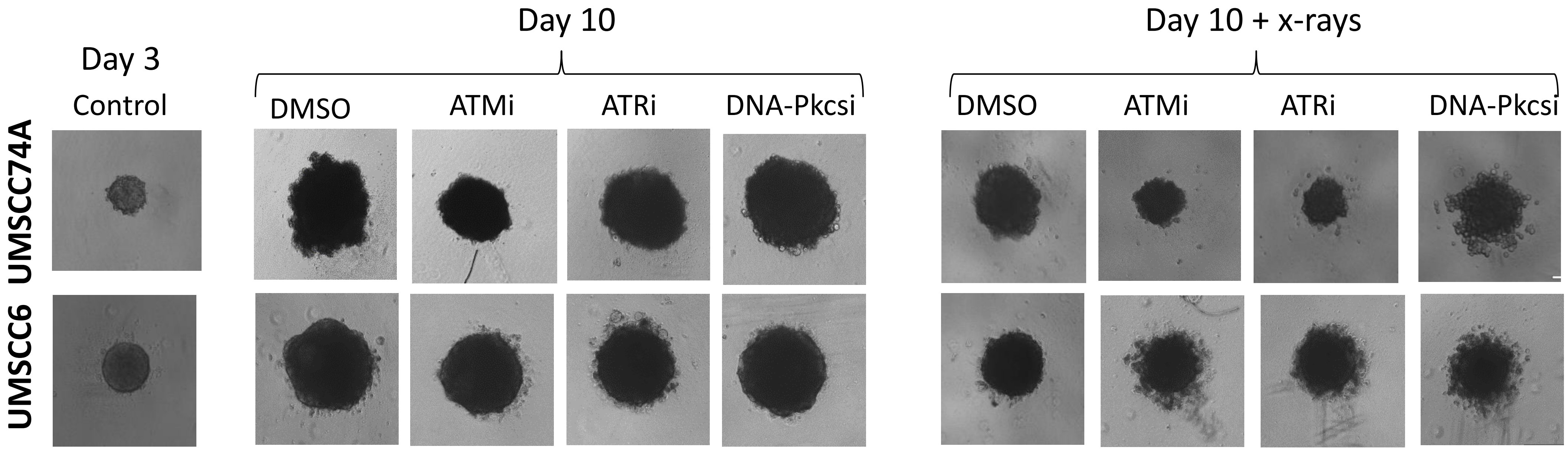


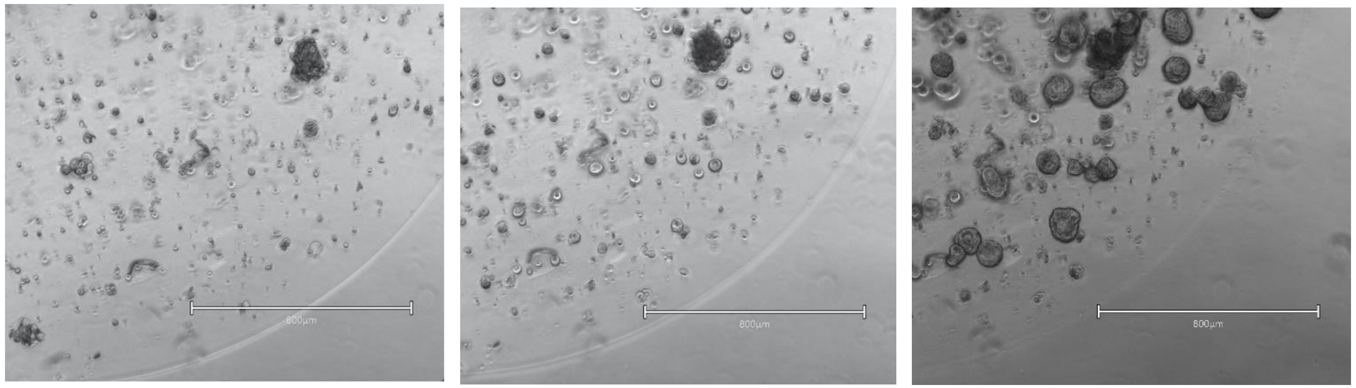




Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*

Utilising 3D models of HNSCC with photons and protons





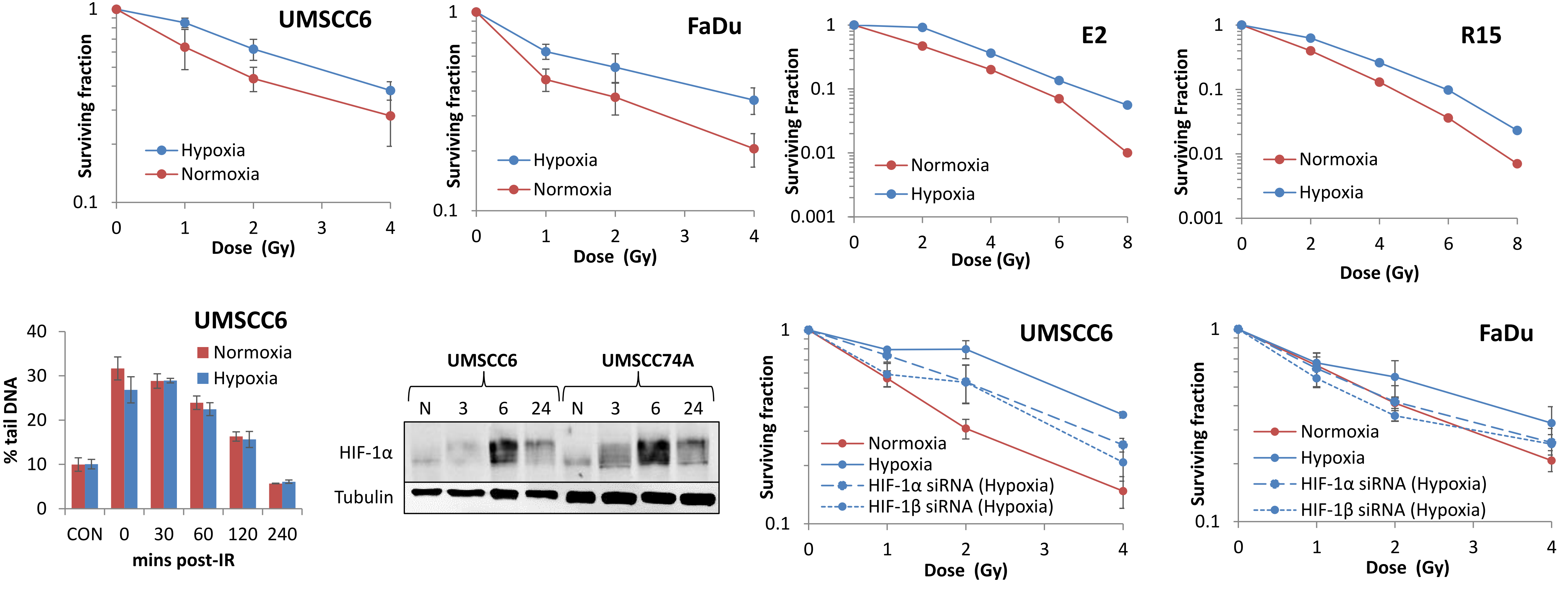
Day 1 **Day 4** **Day 8**

T1 organoid at Days 1-8 (Emma Melia)

Collaboration with Else Driehuis and Hans Clevers

Vitti and Parsons (2020) ***Cancers***
Zhou et al (2022) ***Front Oncol***

Hypoxia induces significant radioresistance in HNSCC and GBM cells in a HIF-dependent manner



Hill *et al.*, (2022) *Cancers*
Hill, Frost, Rocha *et al.*, *(Unpublished)*

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Examining the radiobiology of FLASH high-LET radiation.

- Using ultra high-dose rates (>40 Gy/s; versus ~5 Gy/min).
- FLASH stimulates normal tissue sparing.
- Mechanism of action unclear (oxygen, radicals or metabolism?).
- Opportunity for utilisation of FLASH protons/particles.

Favaudon *et al* (2014) *Sci Trans Med*

Vozenin *et al* (2018) *Clin Cancer Res*

Collaborations with Stuart Green, Tzany Wheldon, Ben Phoenix and Kristoffer Petersson

Bourhis *et al* (2019) *Radiother Oncol*

Hughes and Parsons (2020) *Int J Mol Sci*

R01CA256854-01

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Some key biological questions to be addressed

- More substantial investigations into the radiobiology of particle ions with increasing LET in defined 2D/3D preclinical normal/tumour model systems.
- To investigate novel beam delivery (e.g. FLASH and minibeams) and to define the biology behind these phenomenon.
- Examine clinically-relevant dose fractionation experiments in relevant *in vitro* and *in vivo* preclinical models.
- Investigate combinatorial treatments (e.g. targeted DDR/IO drugs and inhibitors, perform high-throughput screening experiments) for tumour radiosensitisation and normal tissue radioprotection.

More effective and efficient translation of radiobiology research into particle ions from the lab and into the clinic for patient benefit.