The LhARA radiobiology programme: RBE variability with LET

Professor Jason Parsons
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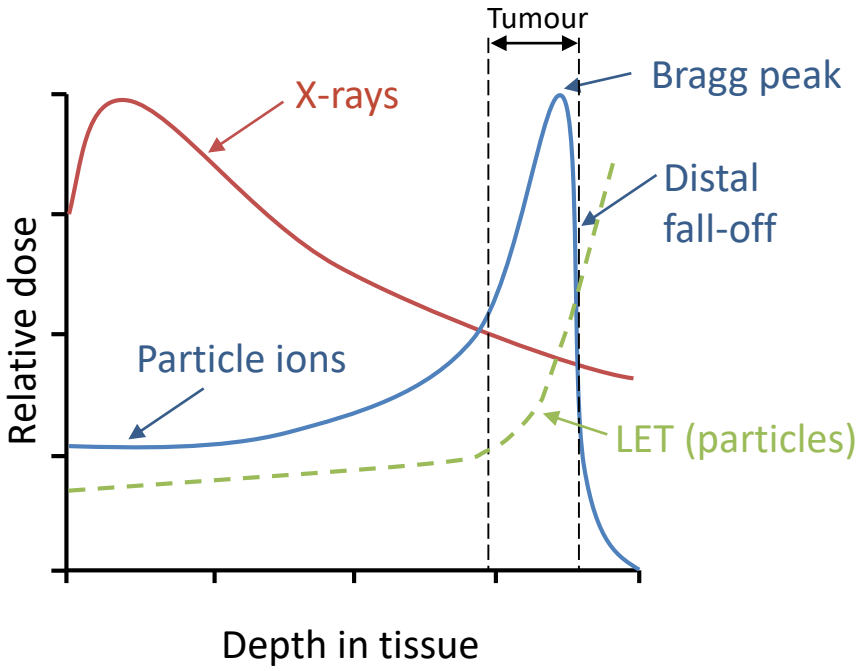
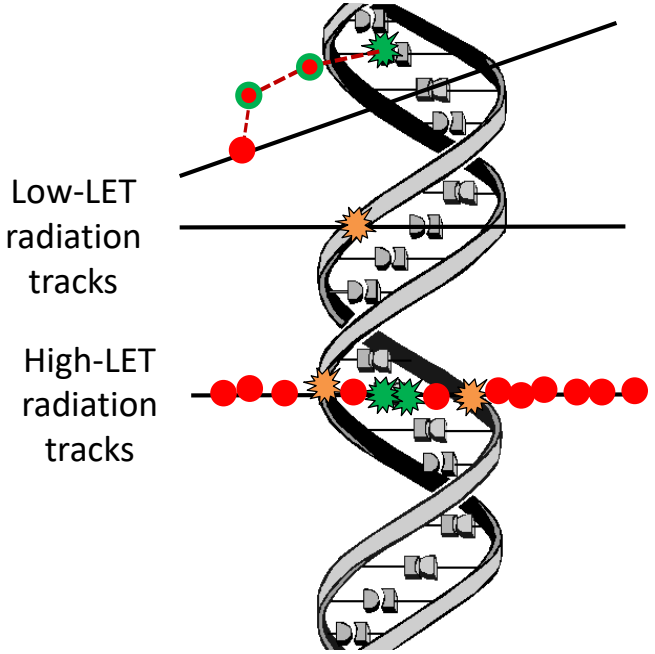
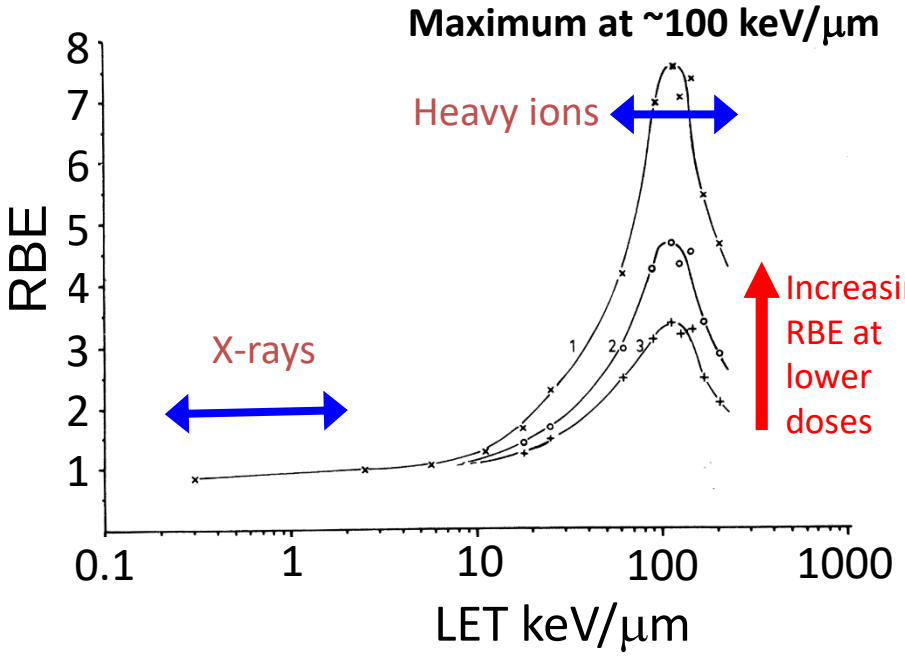
University of Liverpool

The biological uncertainties following particle ion therapy associated with LET







- Linear energy transfer (LET) increases at and around the Bragg peak, leading to an enhanced relative biological effectiveness (RBE).

Vitti and Parsons (2019) *Cancers*

Relative biological effectiveness (RBE) is not constant

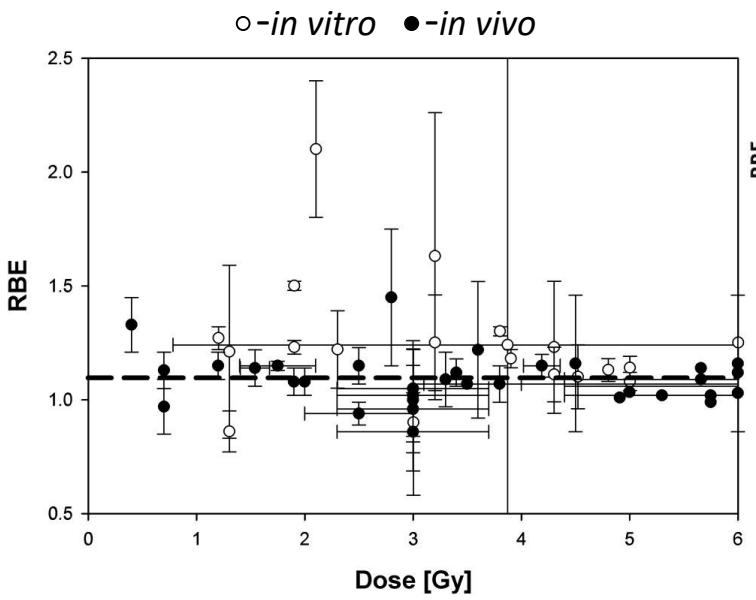
- In proton beam therapy, a constant RBE of 1.1 is assumed, although this is highly debated.
- RBE depends on many physical (ion type, dose, dose rate, energy, LET) and biological (tumour type, inherent radiosensitivity, tumour volume, tumour hypoxia) factors.
- RBE for carbon ions ranges from ~1.3-3.2 in normal and tumour tissues (Karger and Peschke, 2018, *Phys Med Biol*).
- Higher RBE will inevitably occur at the distal end of the Bragg peak.
- RBE of protons, and other high-LET radiation, should be considered as a continuous variable rather than constant.

What are the implications for using an incorrect RBE?

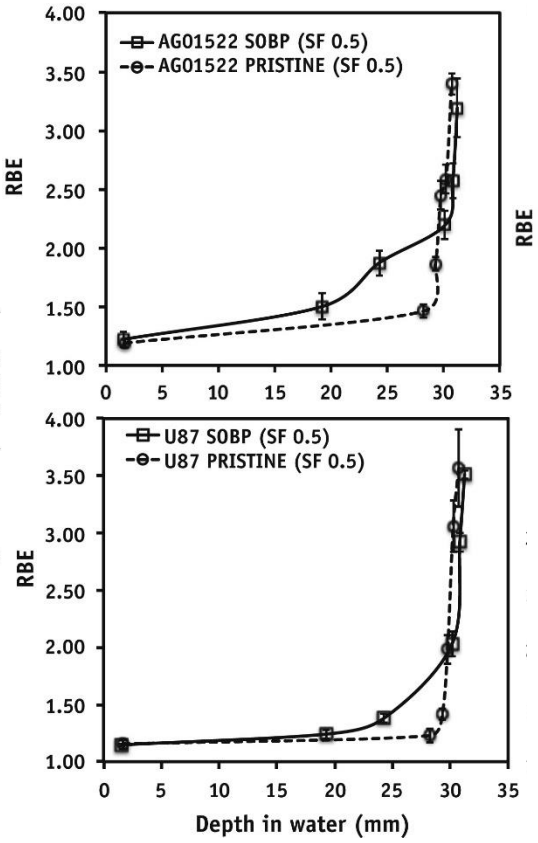
- Particle ions are not utilised to their full capacity, and under dosing of specific tumours.
- Potential unnecessary increases in radiation dose to the surrounding normal tissues and organs at risk.
- Lack of desired clinical outcome relating to effective tumour cell killing and optimal patient survival.

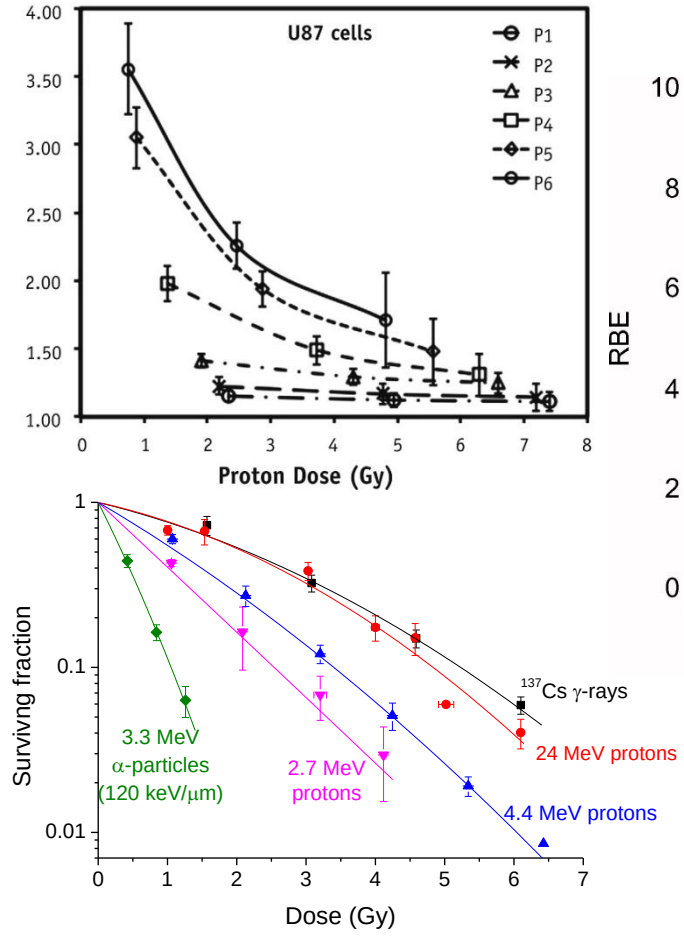
Variabilities in RBE of proton and heavy ions

Chaudhary et al., (2014) IJROBP

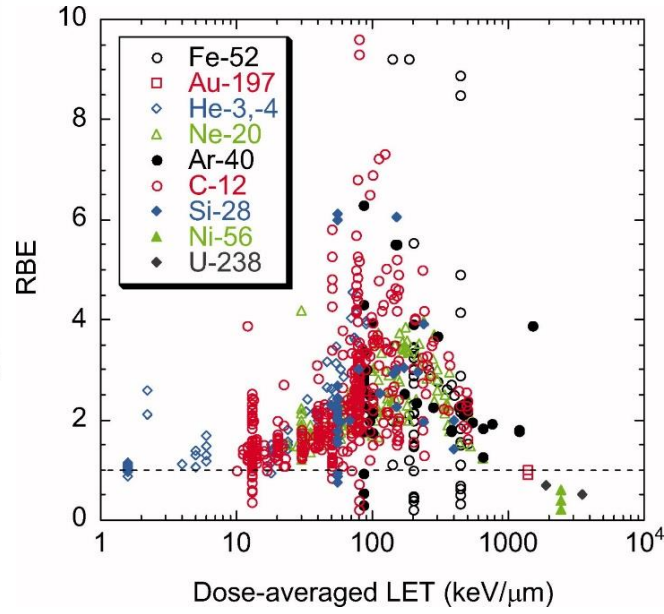


Paganetti and van Luijk (2013) Sem Rad Oncol





Courtesy of Mark Hill



Ando and Kase (2009) Int J Rad Biol

- Further demonstration that RBE is highly dependent on LET (relative to the Bragg peak) and on ion species, dose and model (tumour/normal) used.

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

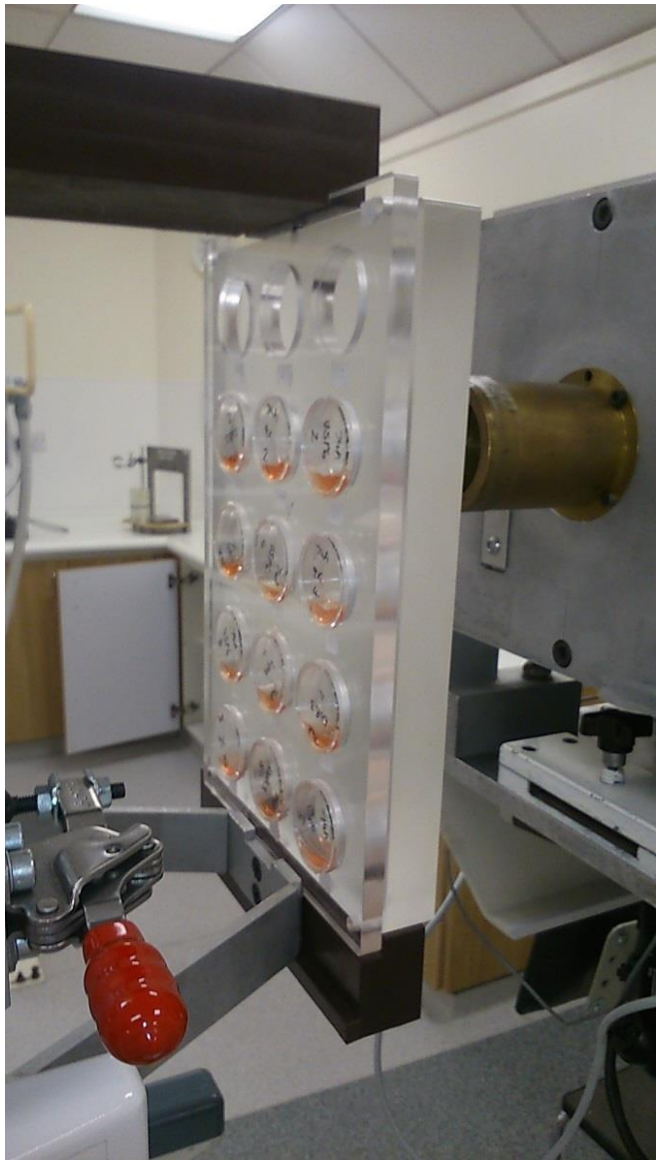
MRC Medical Research Council

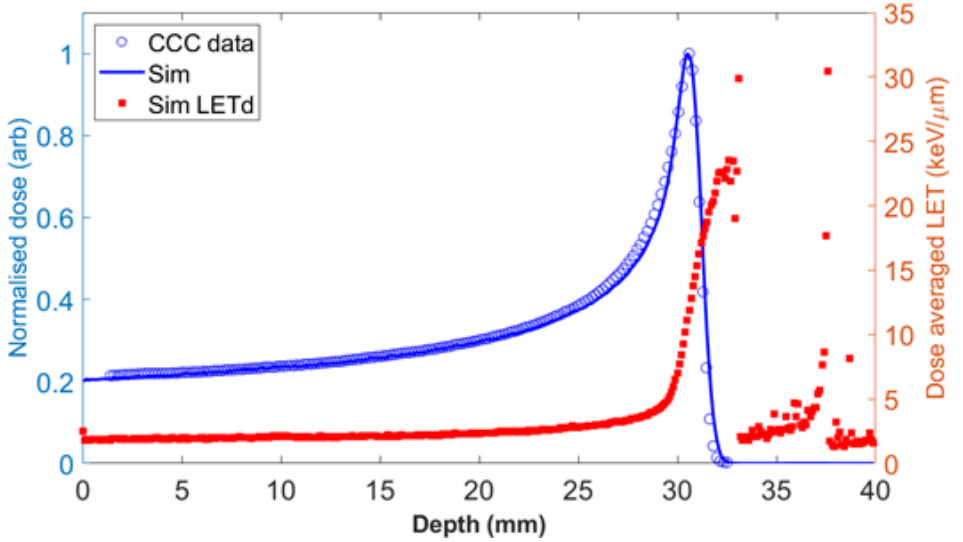
north west cancer research
Putting our region's cancer needs first

R01CA256854-01

NIH National Institutes of Health
Turning Discovery Into Health

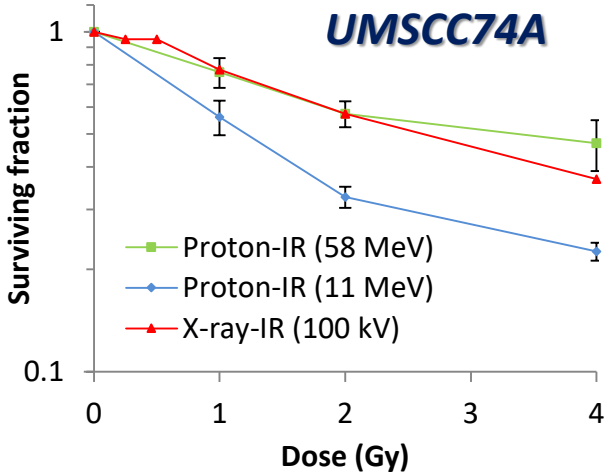
Understanding the radiobiology of protons using the 60 MeV cyclotron at the Clatterbridge Cancer Centre



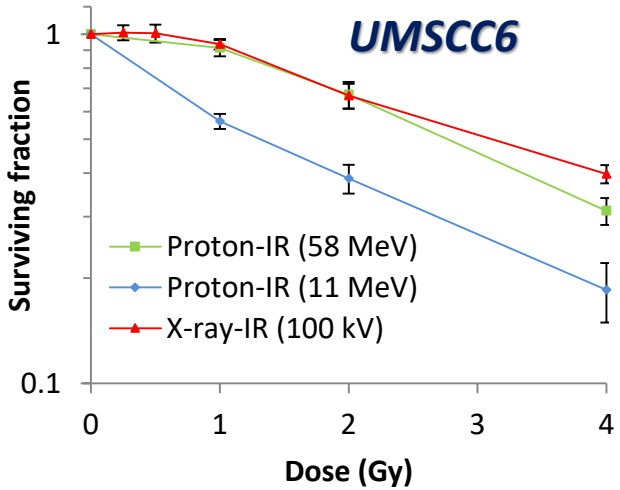


Jacinta Yap, Carsten Welsch

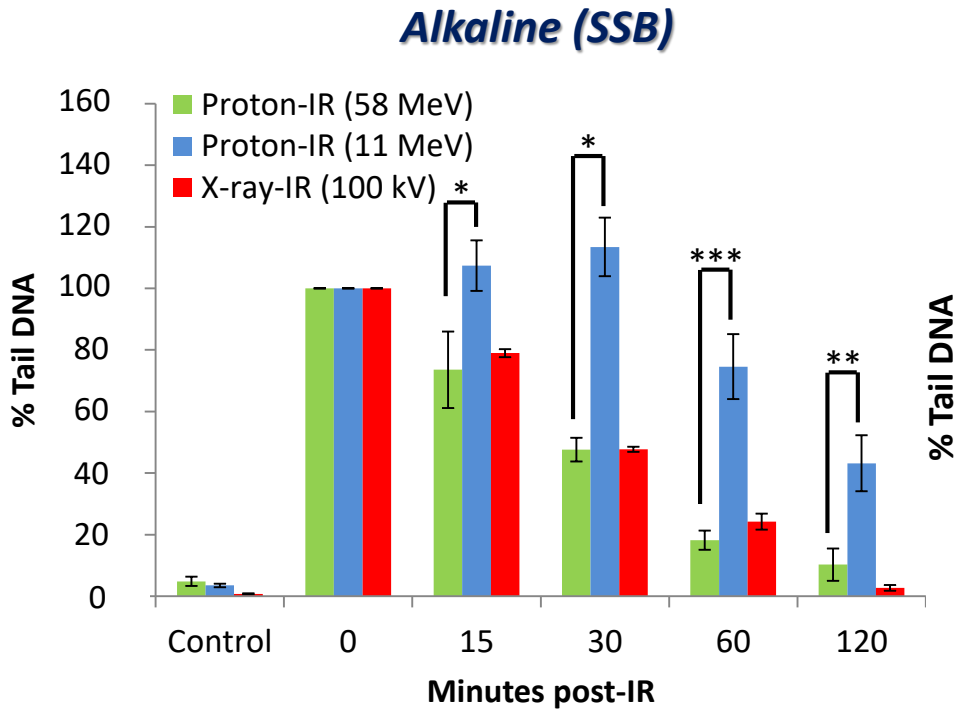
“Relatively” high-LET protons cause a decrease in HNSCC cell survival due to CDD formation compared to low-LET protons



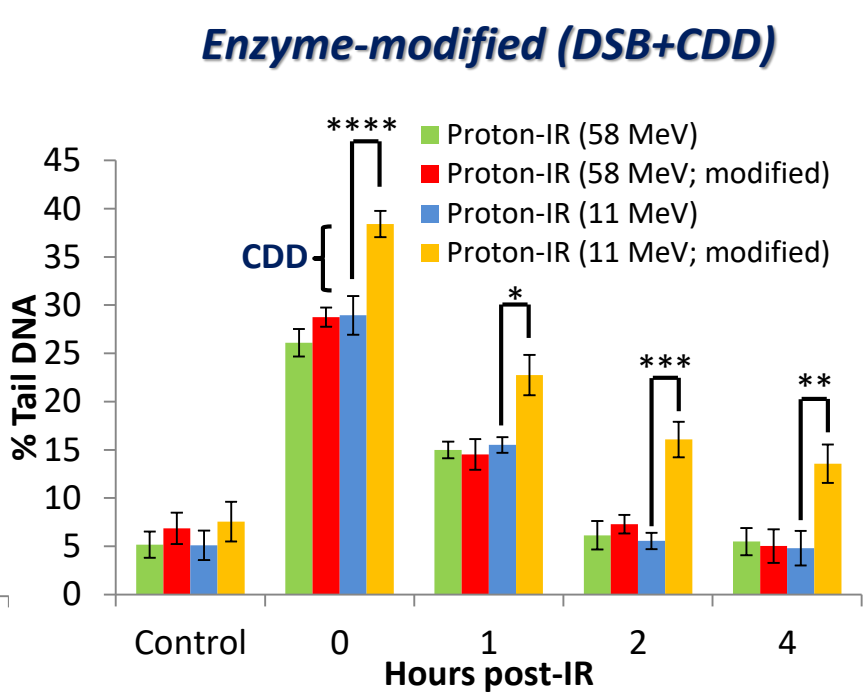
SF2, p<0.02; RBE=1.7



SF2, p<0.01; RBE=1.9



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

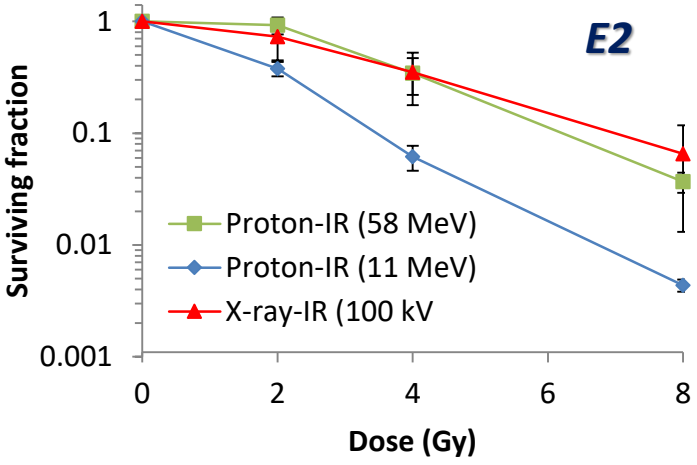


*p<0.02, **p<0.01, ***p<0.005, ****p<0.001

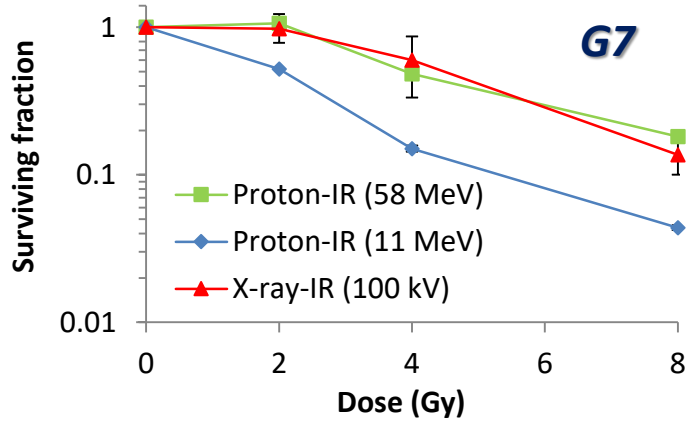
58 MeV (1 keV/µm); 11 MeV (12 keV/µm)

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

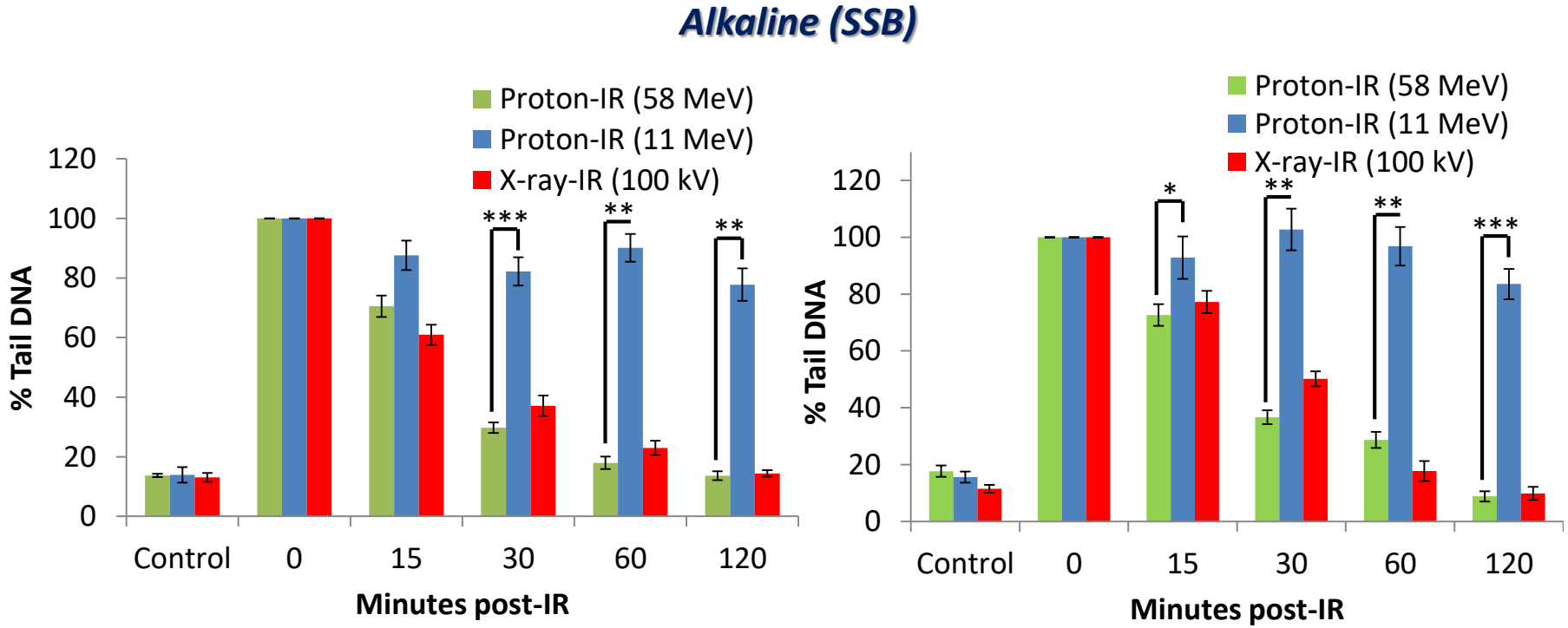
“Relatively” high-LET protons cause a decrease in GBM cell survival due to CDD formation compared to low-LET protons



SF2; RBE=2.4



SF2; RBE=2.0

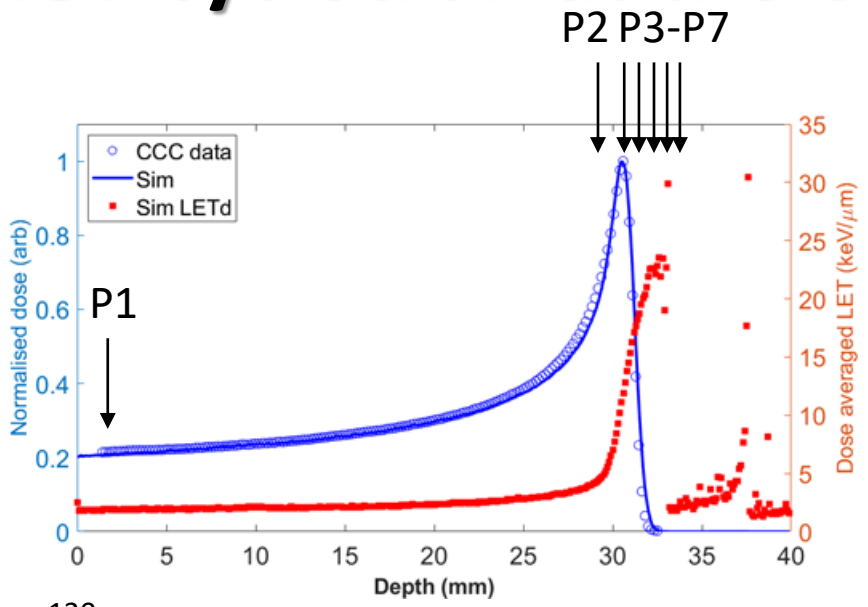


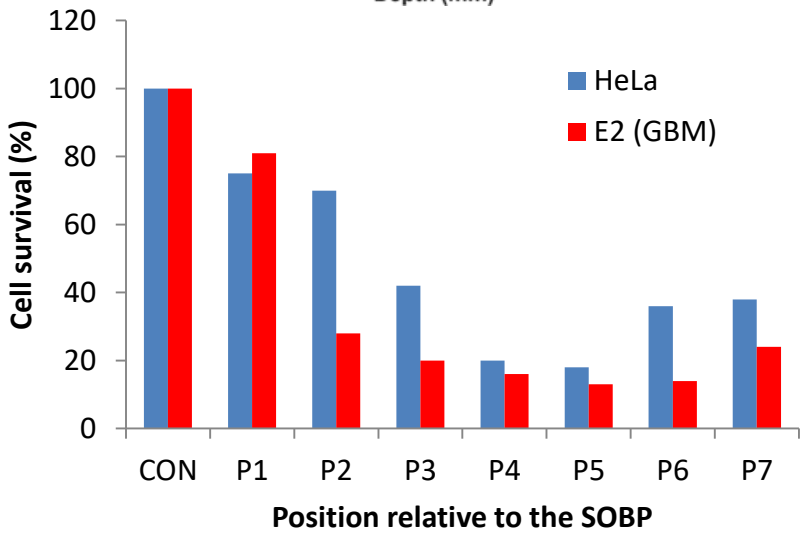
*p<0.02, **p<0.005, ***p<0.002

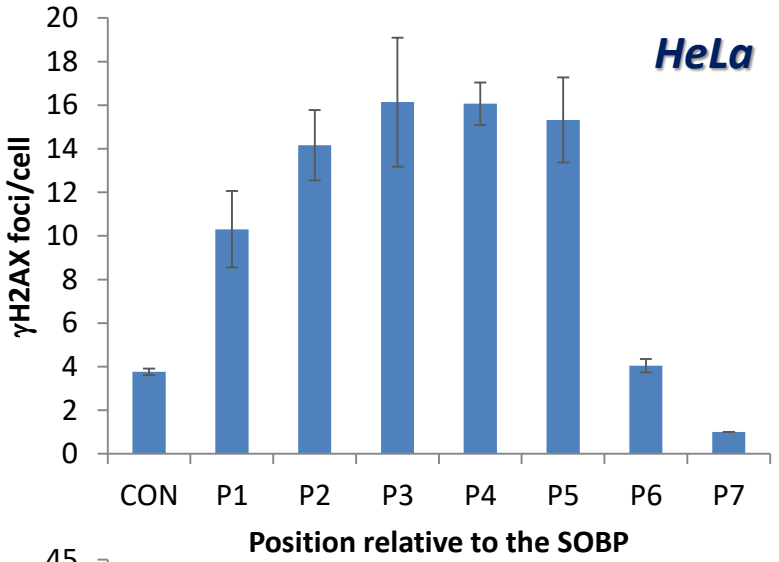
58 MeV (1 keV/µm); 11 MeV (12 keV/µm)

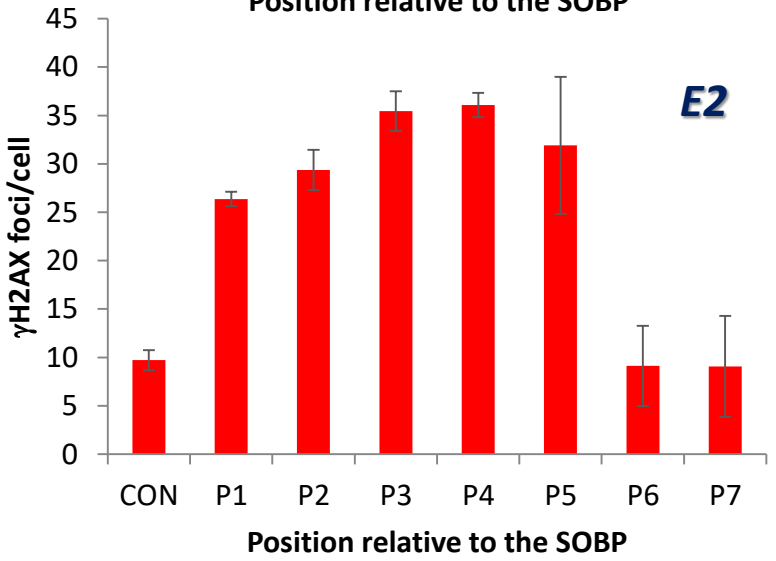
Aiyappa-Maudsley, Chalmers *et al., (Unpublished)*

Detailed radiobiological characterisation of the 60 MeV cyclotron at the Clatterbridge Cancer Centre



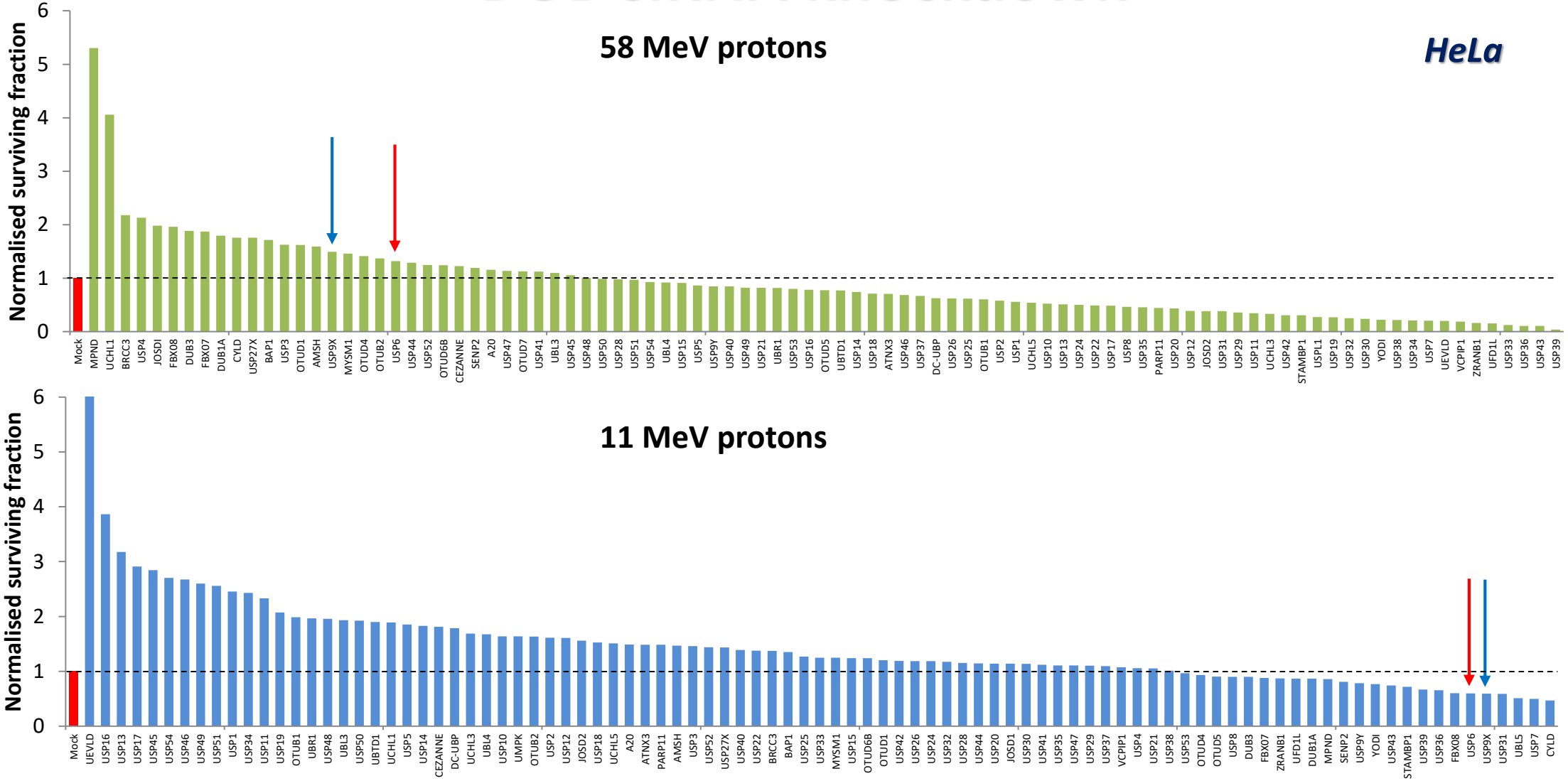






Aiyappa-Maudsley *et al., (Unpublished)*

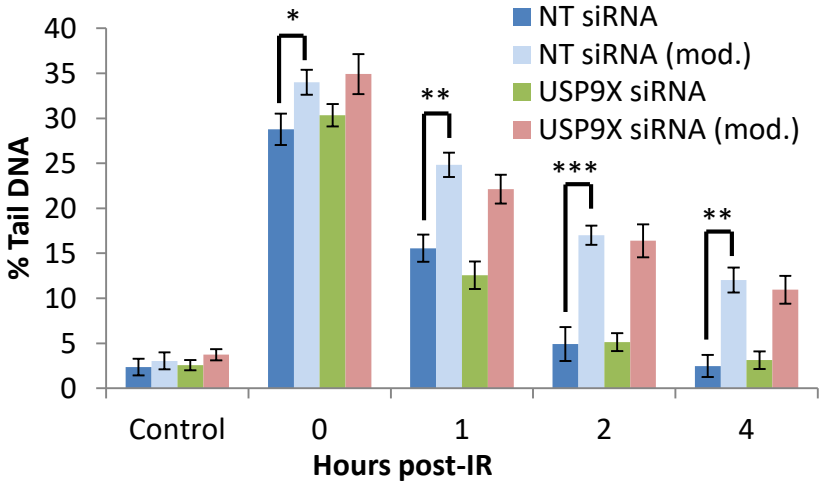
Modulation of proton-induced cellular sensitivity following DUB siRNA knockdown

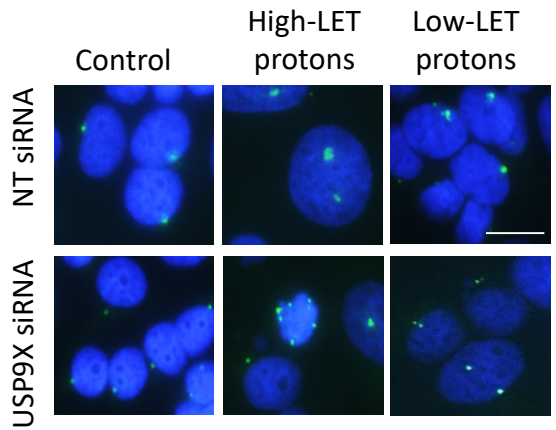


Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*

Nickson, Fabbrizi *et al.*, (2021) *Front Oncol*

USP9X modulates centrosome amplification required for cell survival in response to “relatively” high-LET protons





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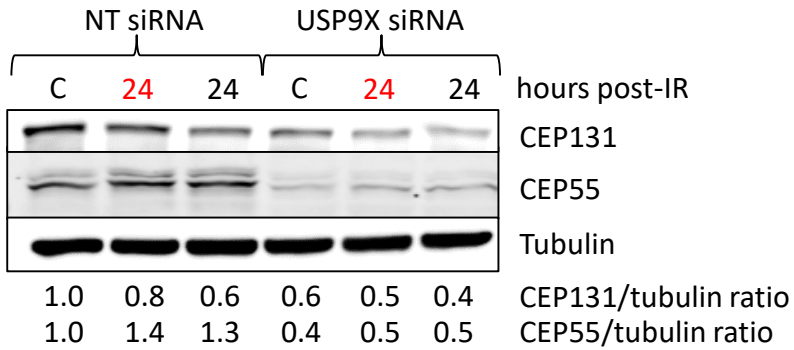
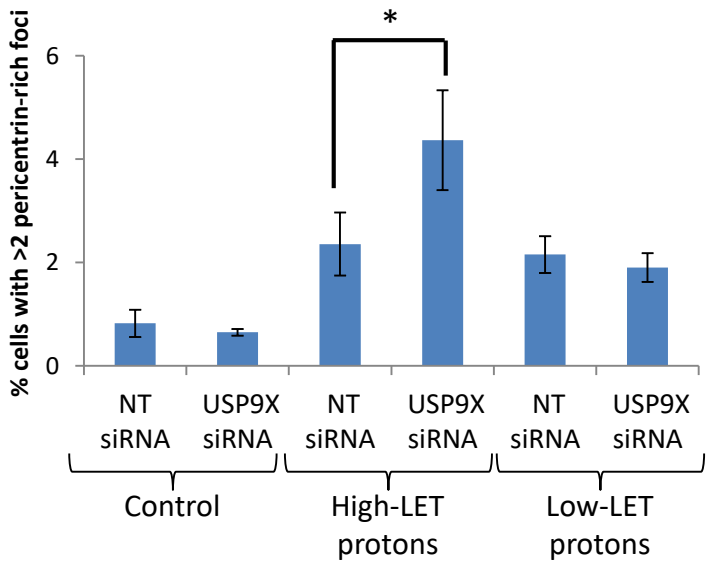
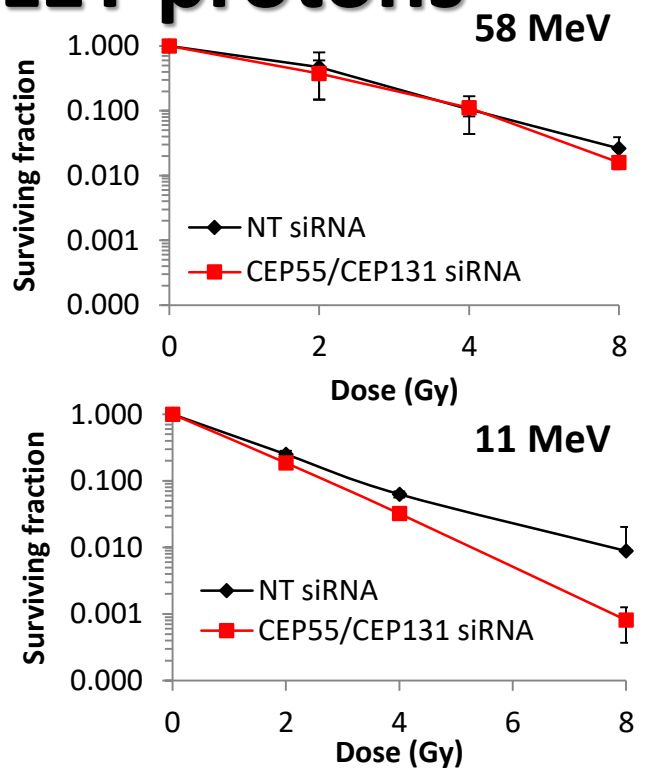
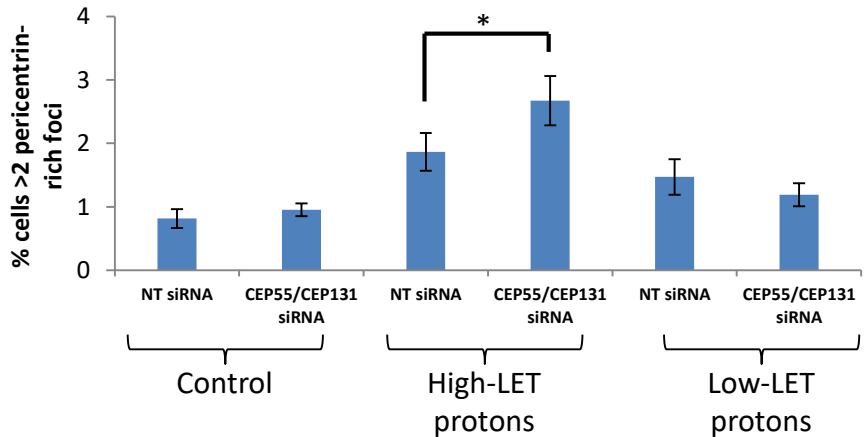






*p<0.05



Nickson, Fabbrizi *et al.*, (2021) *Front Oncol*

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

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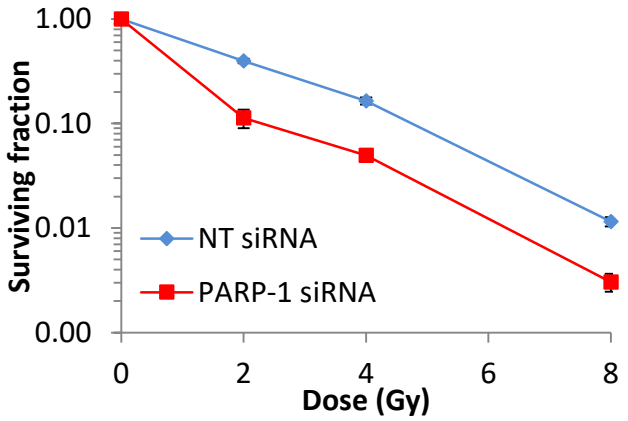
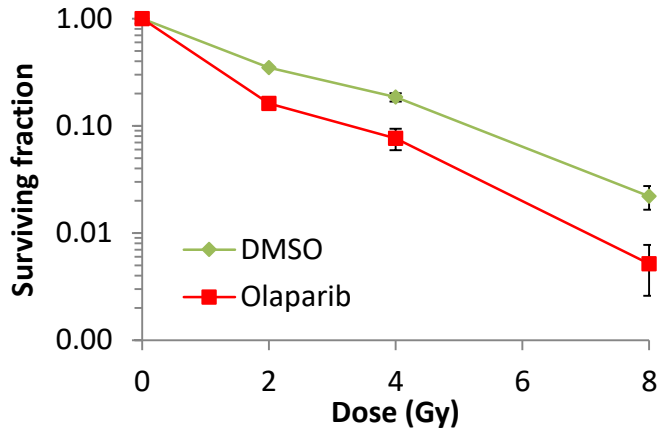
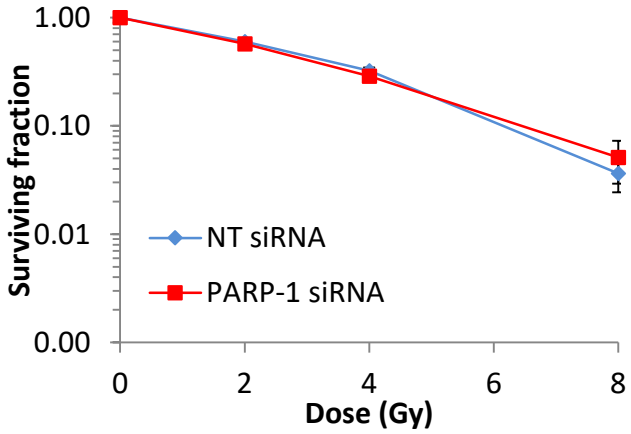
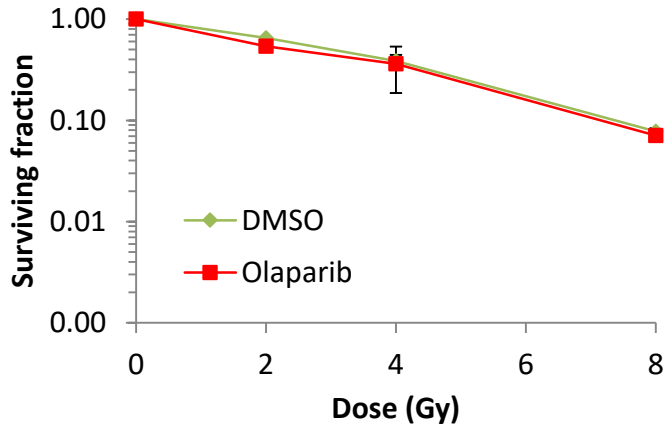
11 MeV

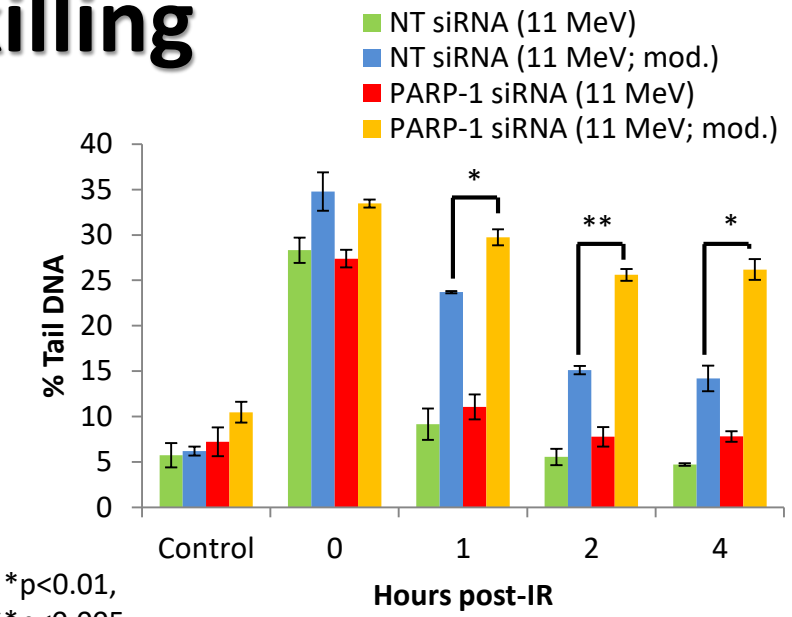




58 MeV







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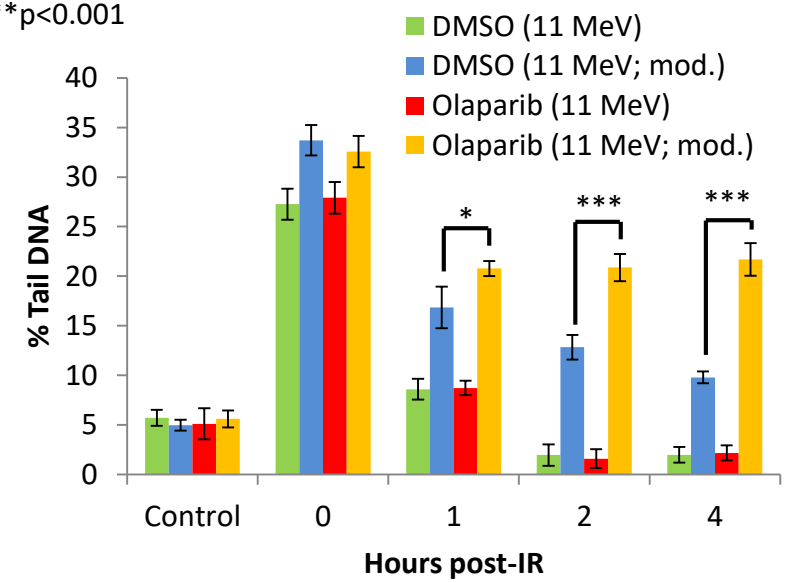
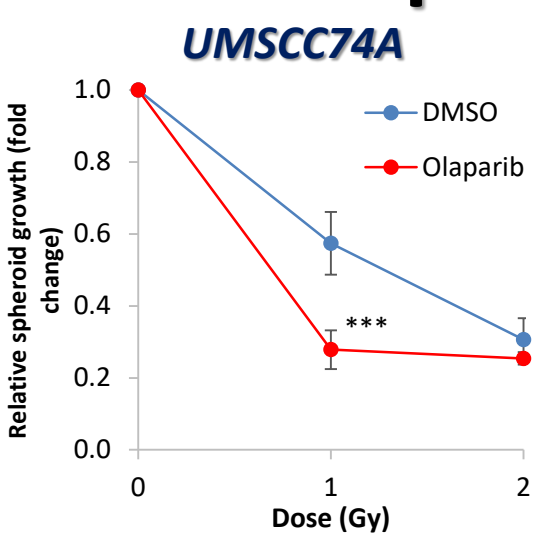
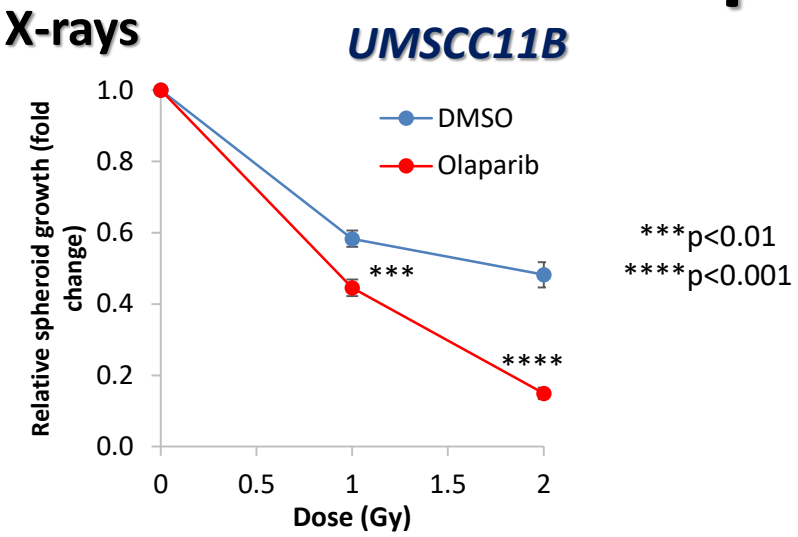
***p<0.001

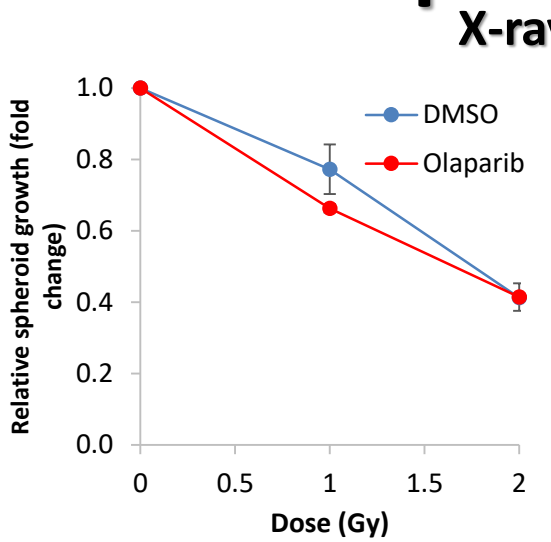


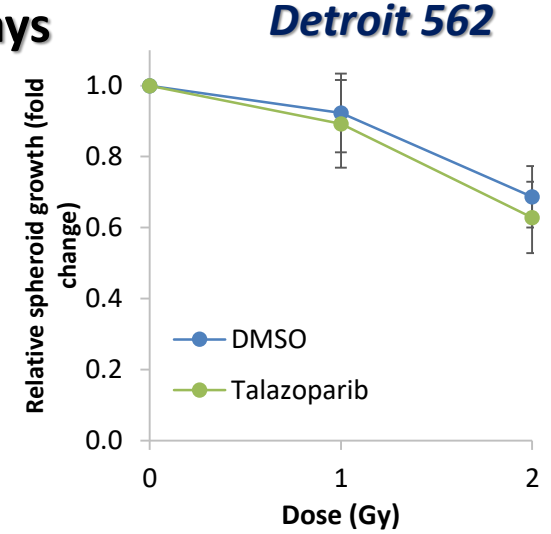
Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*

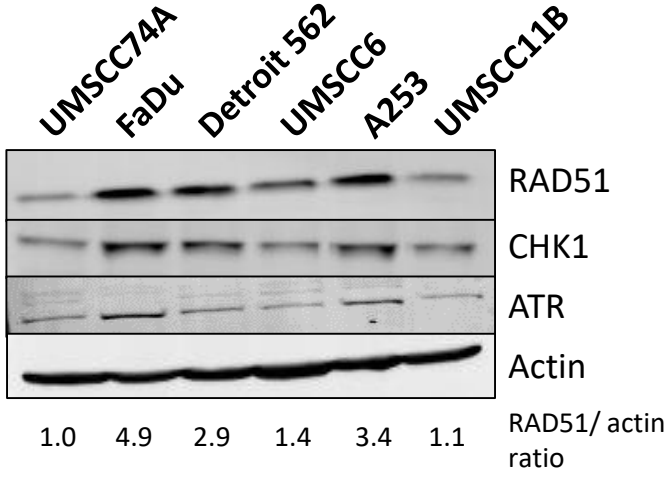
PARP inhibitors can enhance selectively radiosensitise 3D spheroids of HNSCC to photons and protons

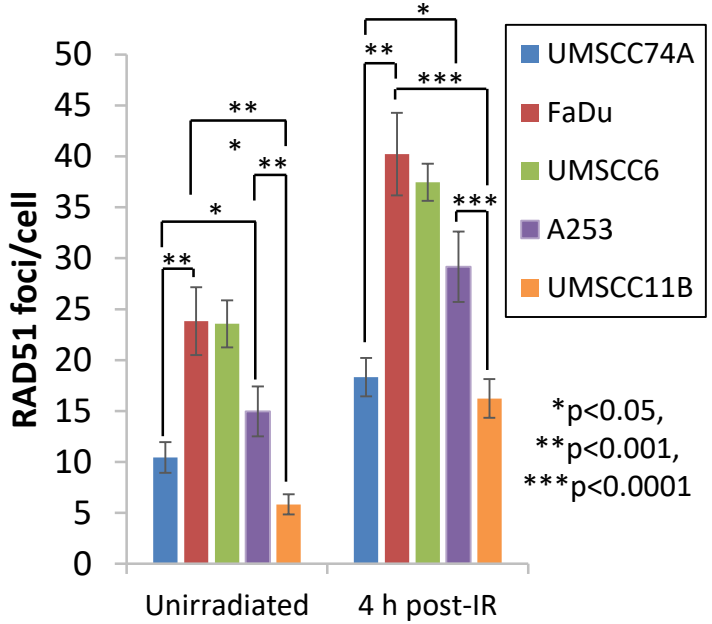


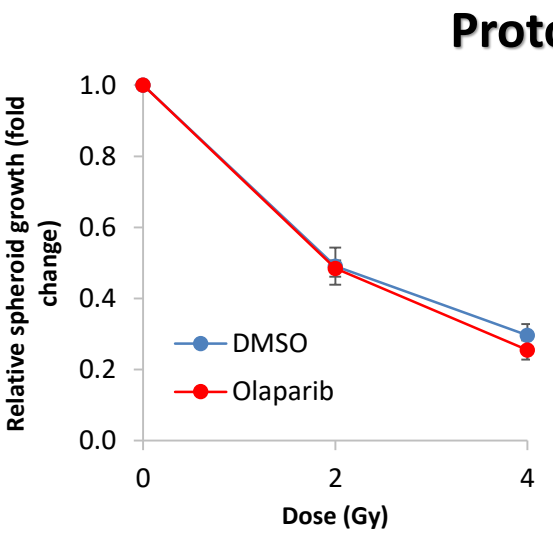


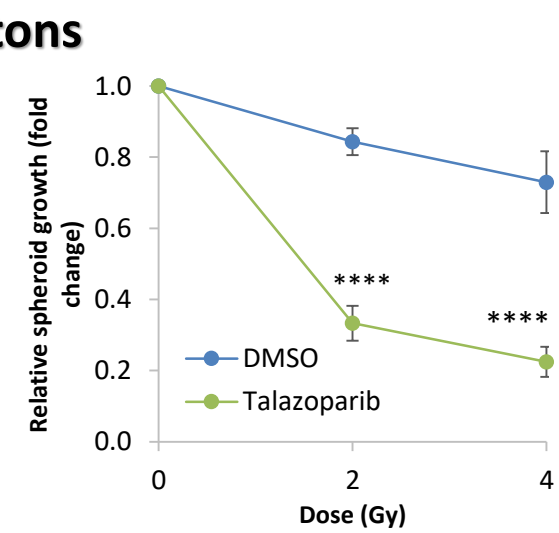












Zhou *et al.*, (2022) *Front Oncol*

Targeting OGG1 and PARG sensitises cells to high-LET protons

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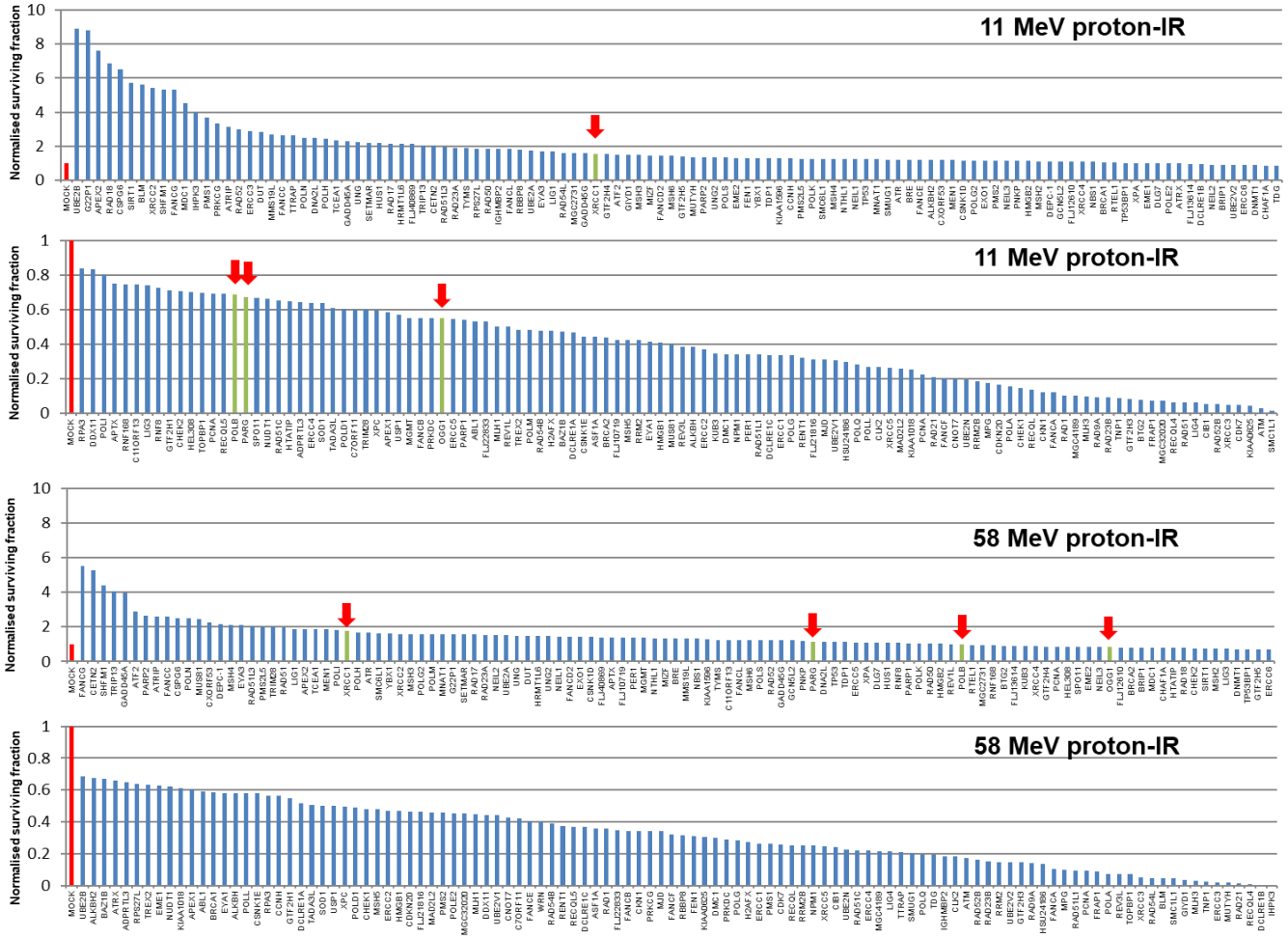

Fabbrizi, Nickson *et al., (unpublished)*

Targeting OGG1 and PARG sensitises cells to high-LET protons

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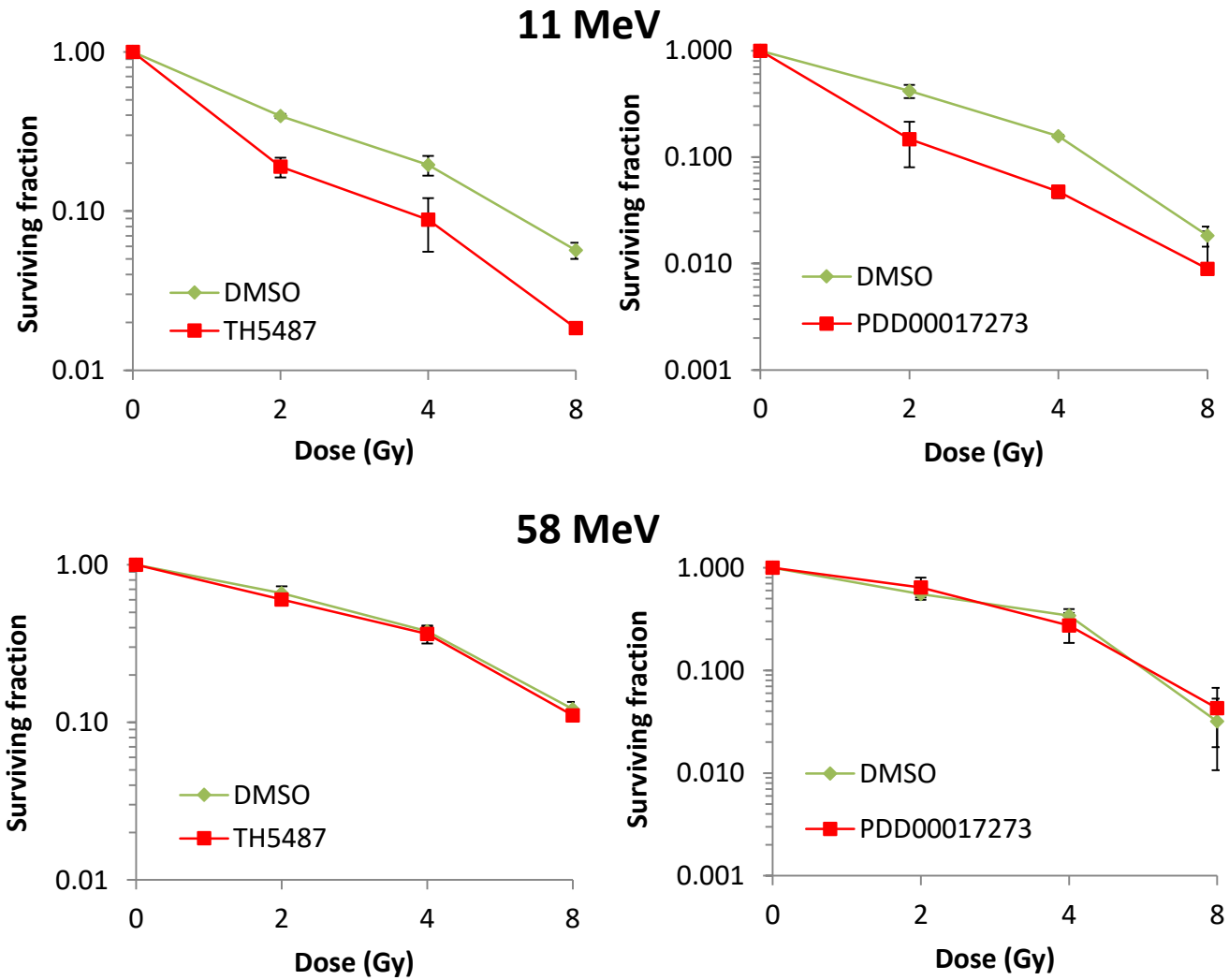
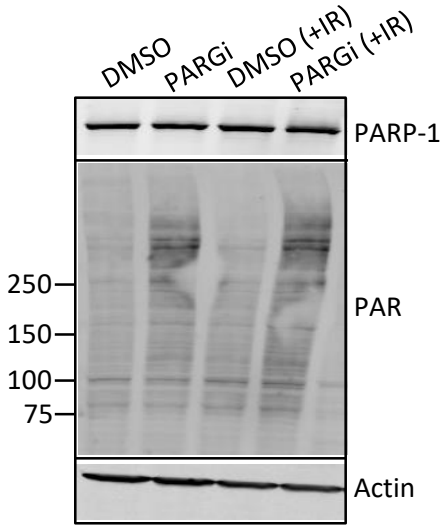
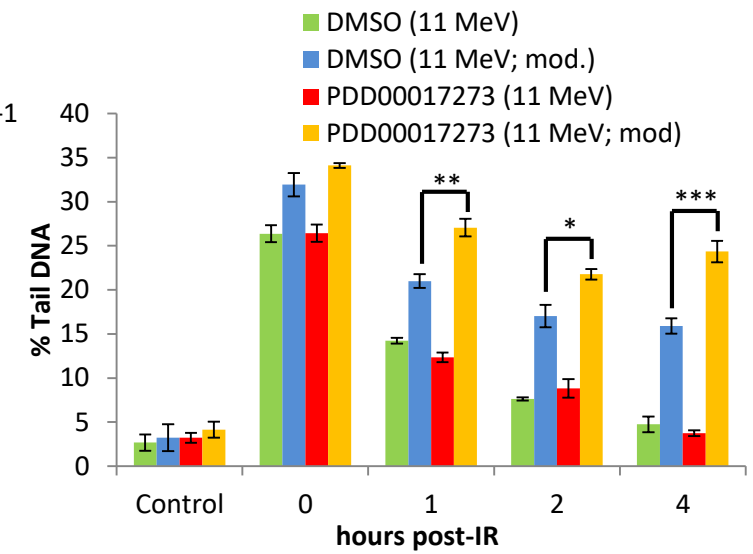
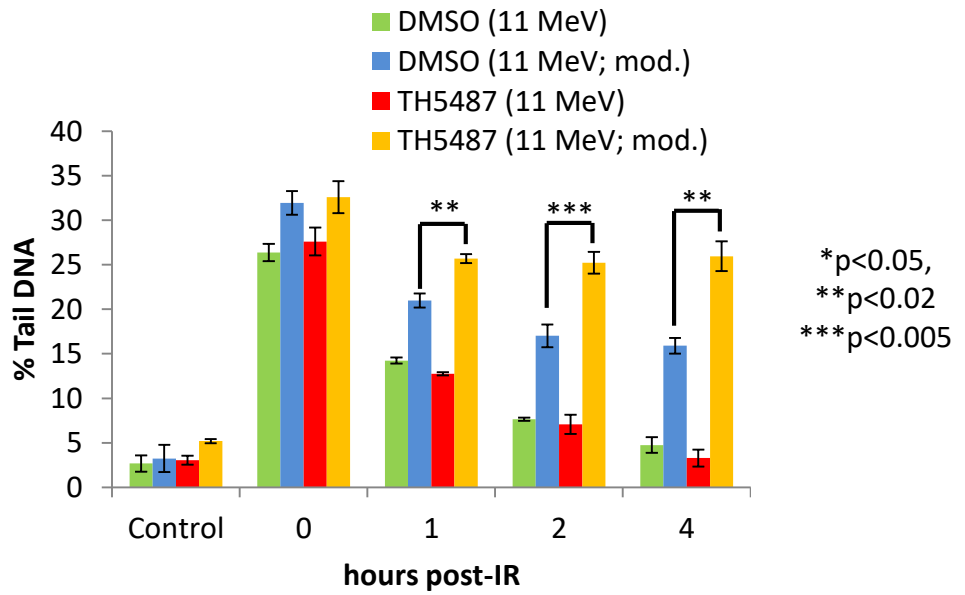




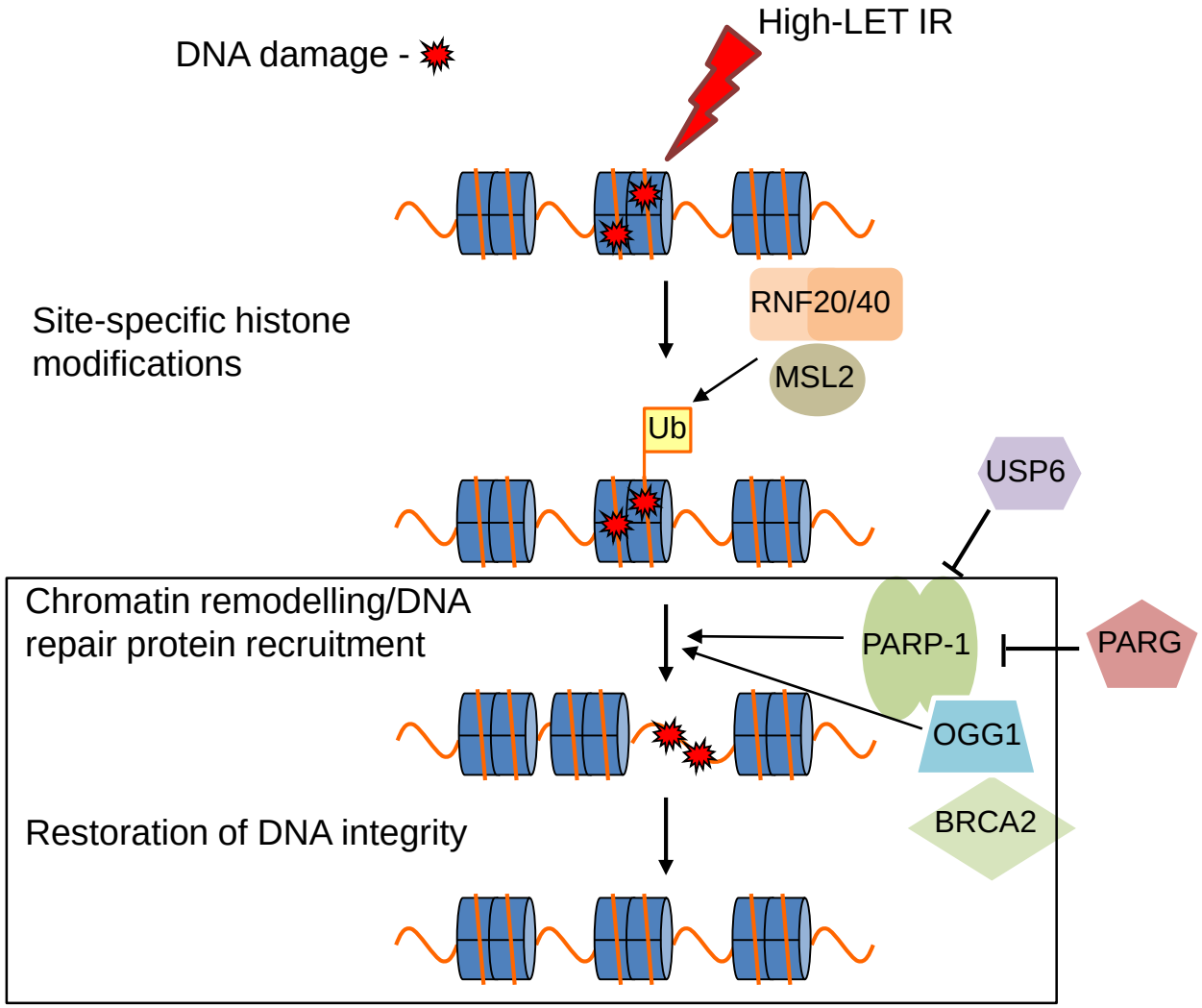




Fabbrizi, Nickson *et al., (unpublished)*

Collaborations with Thomas Helleday and Helen Bryant

Model for the recognition and repair of CDD in chromatin



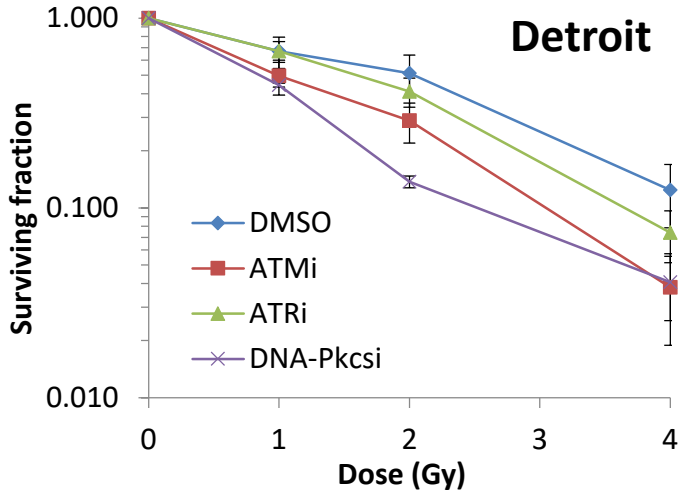
- PBT can have different biological effects depending on where the tumour cells are positioned.
- PBT treatments in the clinic should utilise the high-LET regions for optimal effectiveness.
- High-LET protons can be further enhanced using targeted drugs (e.g. PARP inhibitors).

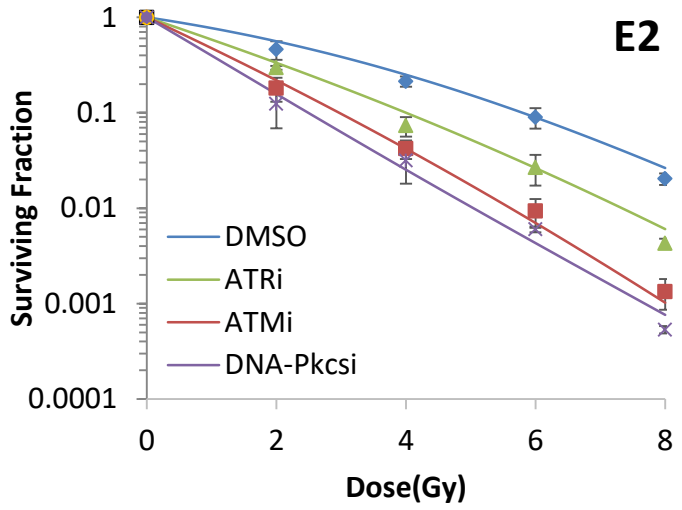
Carter *et al.*, (2018) *Int J Rad Oncol Biol Phys*
Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*
Fabbrizi, Nickson *et al., (unpublished)*

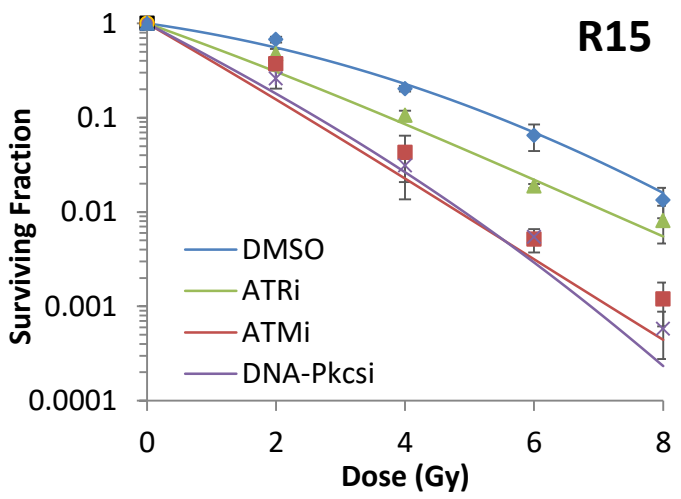
DDR inhibitors can sensitise hypoxic GBM, but not HNSCC, cells to photon irradiation

AZD1390 (ATMi)
AZD6738 (ATRi)
AZD7648 (DNA-Pkcsi)

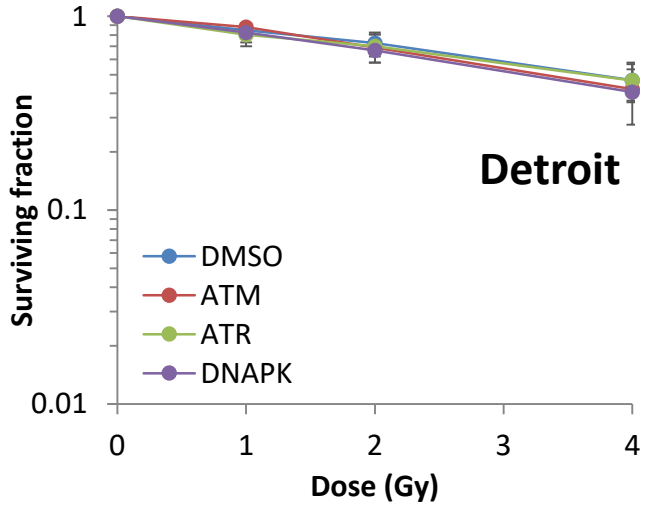
Normoxia

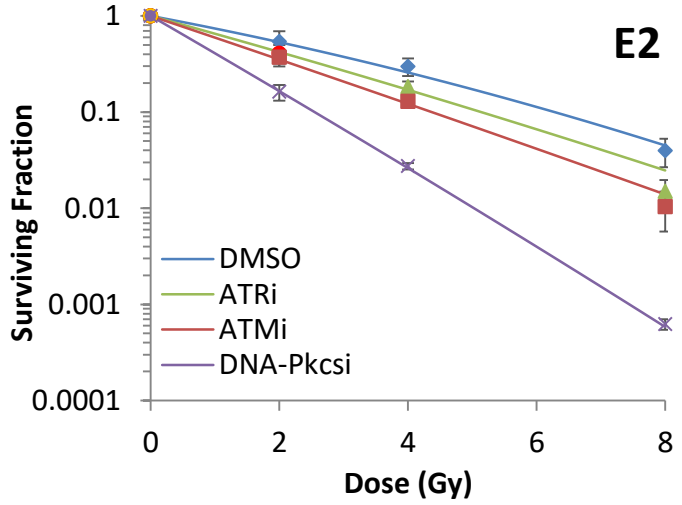


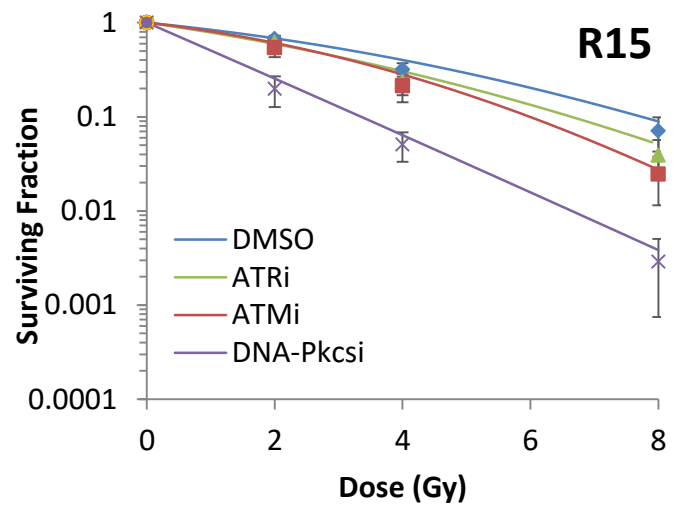




Hypoxia (1 %)







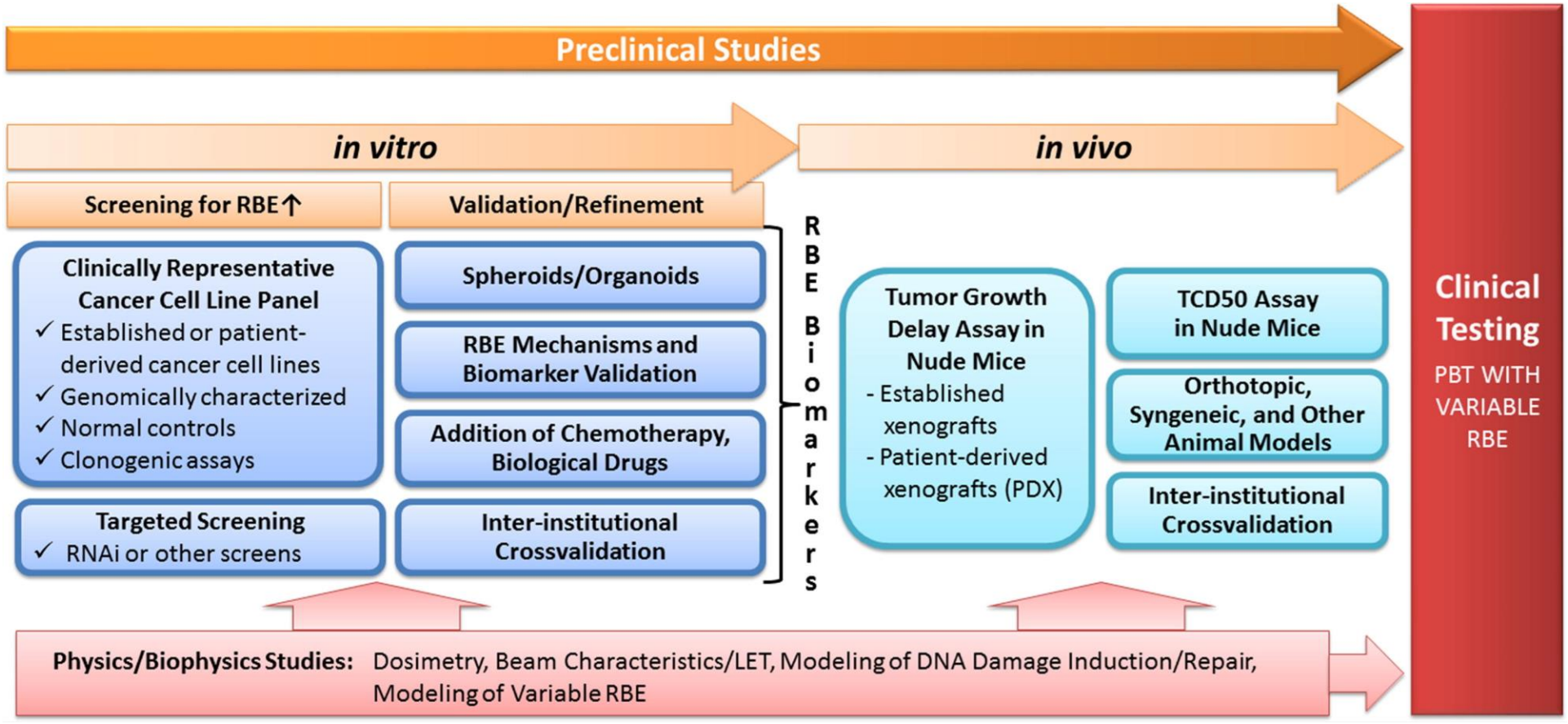
Aiyappa-Maudsley, Zhou, Chalmers *et al., (Unpublished)*

What steps must be taken to understand the RBE of (laser-driven) particle ions

- Substantial *in vitro* and *in vivo* research should establish the changes in RBE with dose in defined normal and tumour cell/tissue types.
- Acquired data (e.g. focussed on cell survival) should be derived from large numbers of experiments to reduce the errors, and from a large number of the same tumour models to exclude cell-specific effects.
- Experiments should also assess the differential response across the Bragg peak and at different energies (relative to LET).
- Importantly, *in vivo* work must be performed to explore the effect of particle ions on more appropriate animal models.

Further research establishing the RBE relative to LET will lead to optimal clinical treatment using particle ions.

Translational pipeline for prediction of variable RBE values



Willers et al., (2018) Radiother Oncol

Summary

Technical advantages of the LhARA facility

- Provides a reproducible, stable and reliable beam critical for acquiring accurate radiobiological data, and for performing systematic evaluations of the biological response.
- Beam which is flexible, easily accessible, and potentially high throughput (unlike clinical facilities).
- Ions can be delivered in very short pulses (10-40 ns) and high repetition rates.
- Ability to deliver particle ions at different energies/LET (protons at 15 and 125 MeV; carbon ions at 30 MeV) and at different dose rates (e.g. FLASH).
- *In vitro* and *in vivo* end-stations both for routine cell culture experiments (with automated handling in controlled environments), but also animal irradiations.
- Stimulate the analysis of more complex biological end-points.
- Potential for live cell imaging, rather than single end-point measurements.

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