UNIVERSITY OF BIRMINGHAM

The radiobiology of protons and high-LET radiation in head and neck cancer and glioblastoma cell models

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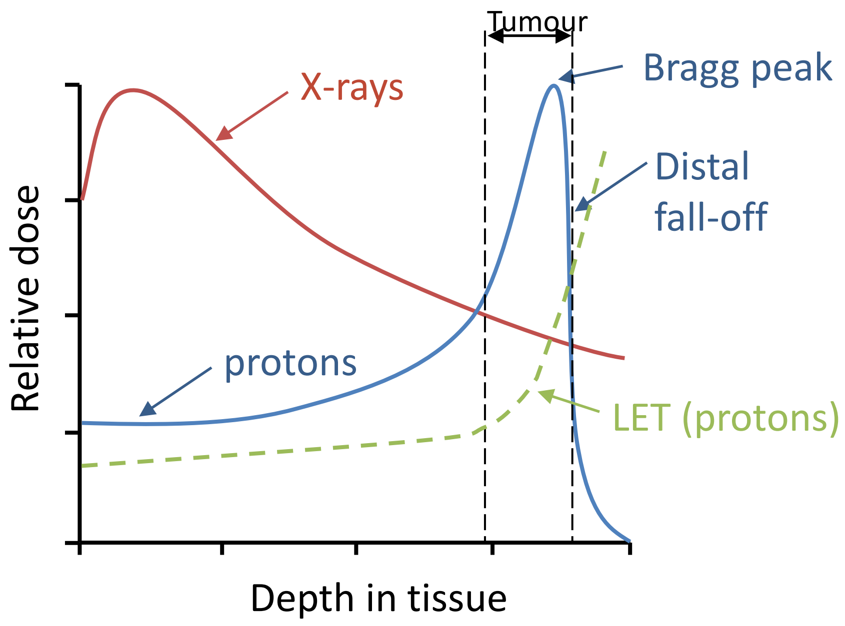
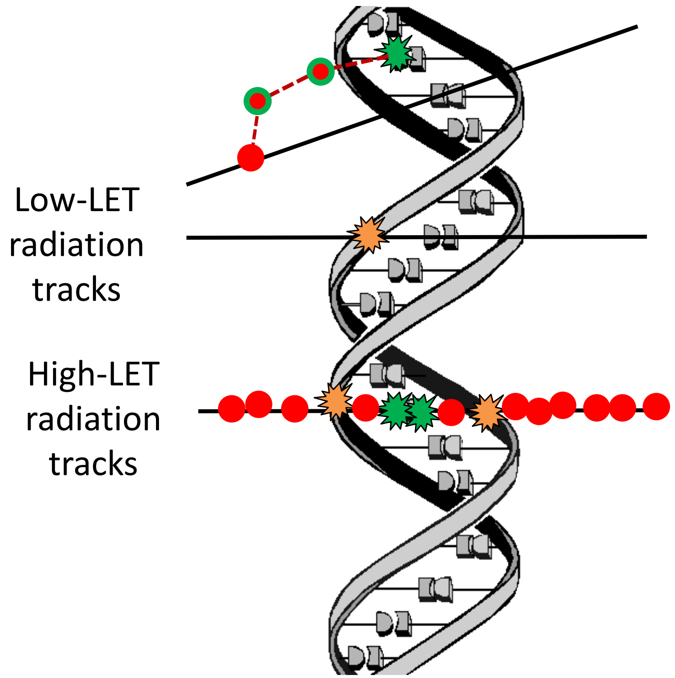
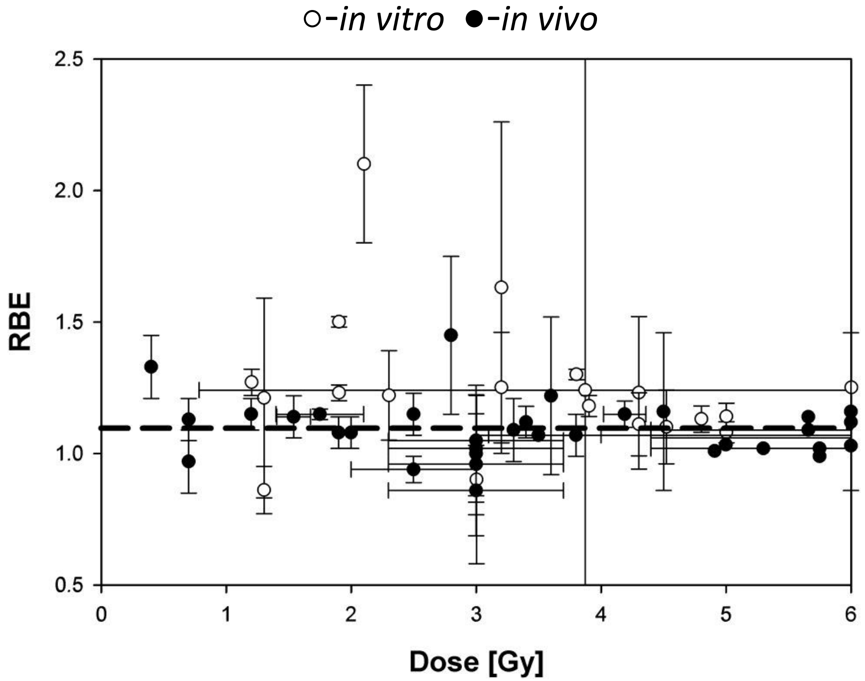
north west cancer research
Putting our region's cancer needs first

The advantages but also biological uncertainties following proton beam therapy (PBT)





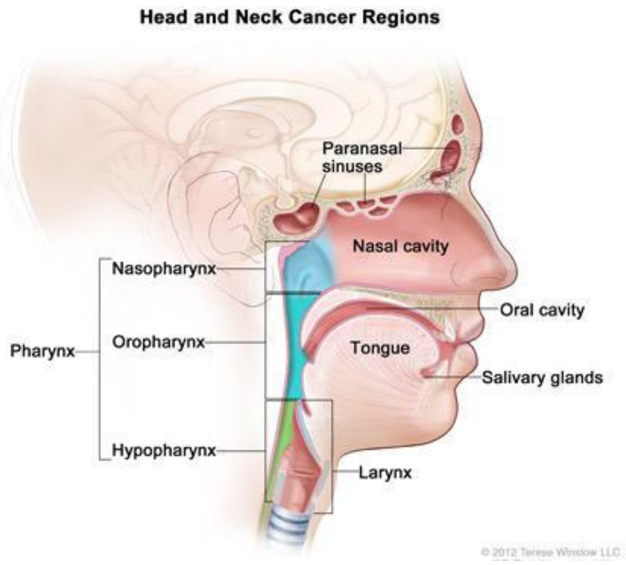


Taken from Paganetti and van Luijk (2013) Sem Rad Oncol

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

Vitti and Parsons (2019) *Cancers*

Head and neck squamous cell carcinoma (HNSCC) and glioblastoma (GBM)

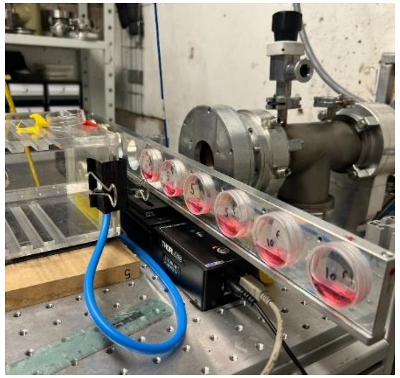


HNSCC

- 6th most common cancer worldwide (~800,000 cases/year).
- Major contributory factors are smoking and drinking.
- Rapid rise in incidence of human papillomavirus (HPV-16) associated cancers of the oropharynx (~60 % of OPSCC and ~40 % of HNSCC combined).
- HPV-positive tumours are more sensitive to radiotherapy and chemotherapy, thus improved prognosis, than HPV-negative tumours.

GBM

- The most common primary brain tumour in adults.
- Survival rates are extremely poor (median of ~12 months).
- Conventional radiotherapy has limited effectiveness.



Zhou and Parsons (2020) *Expert Rev Mol Med;* Aiyappa-Maudsley *et al* (2022) *Neuro Oncol Adv*

Major research questions/aims

- Do protons, particularly at increasing LET, lead to changes in the molecular (DNA) and cellular (survival/RBE) profiles.
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- What is the impact of reduced oxygen (hypoxia) on photon versus proton efficacy.
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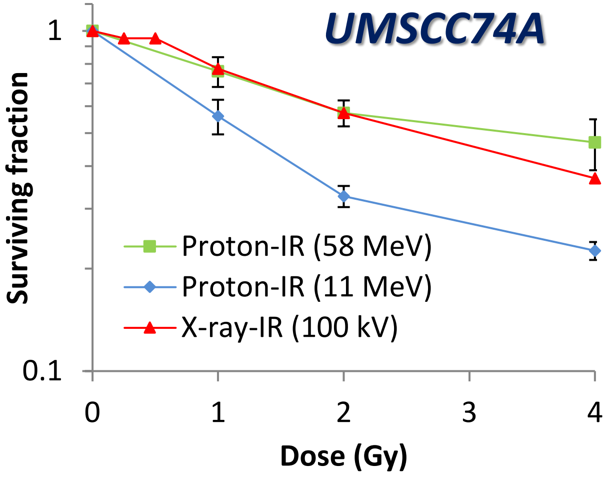
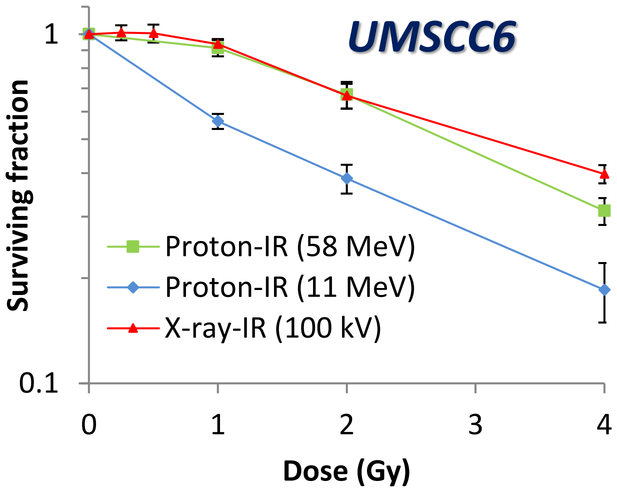
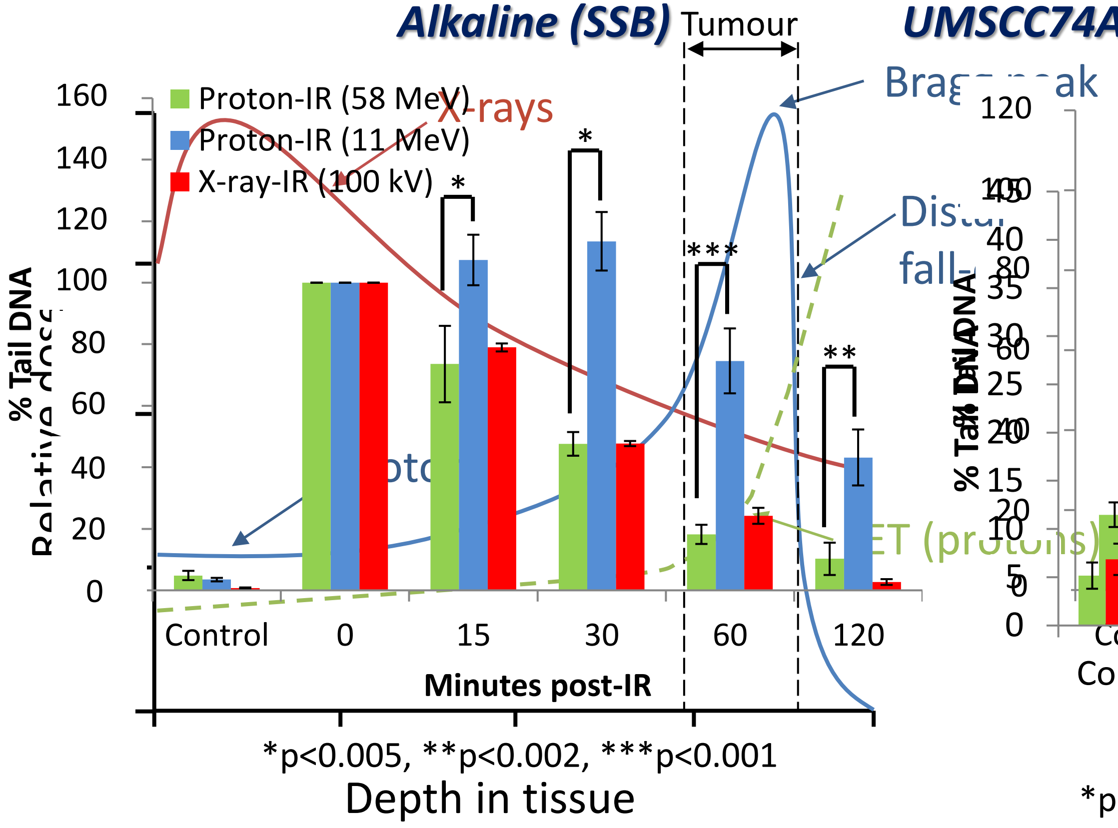
“Relatively” high-LET protons cause a decrease in HNSCC cell survival due to CDD formation compared to low-LET protons

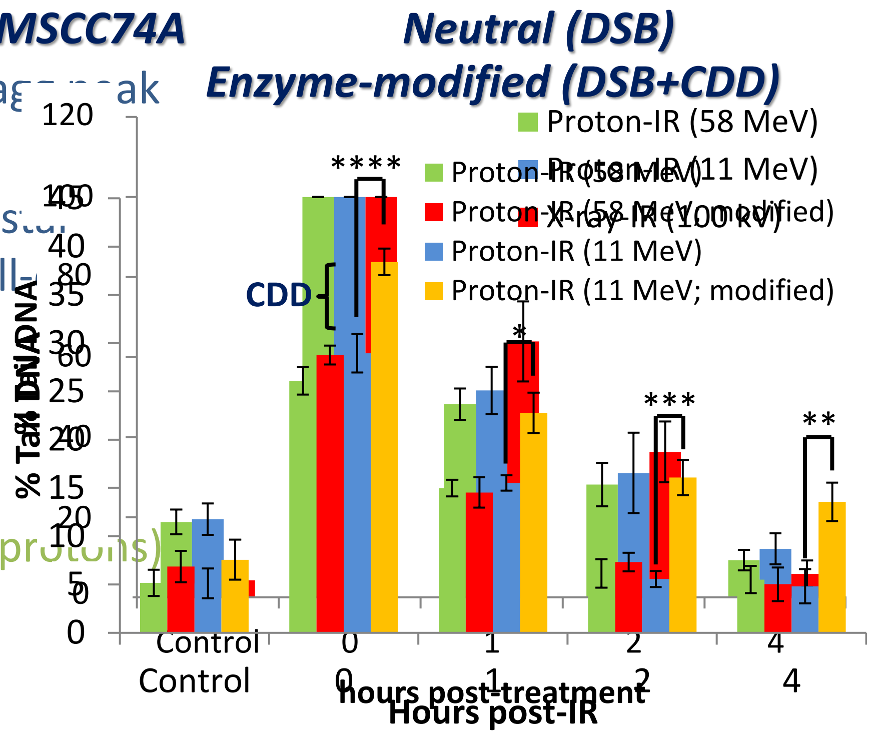


SF2, p<0.02; RBE=1.7



SF2, p<0.01; RBE=1.9



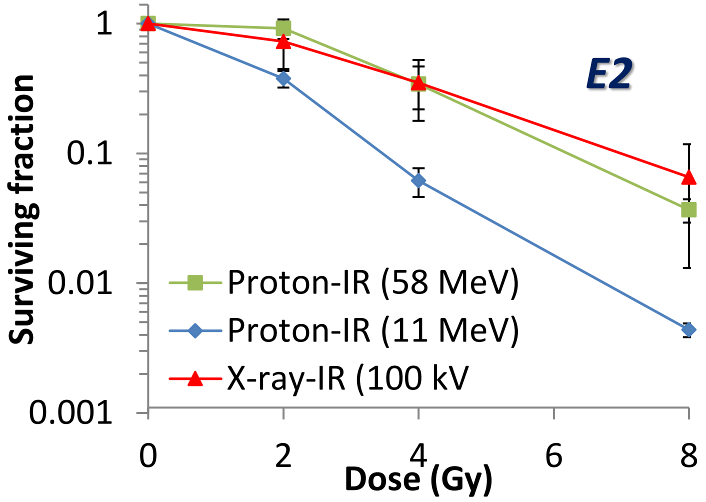


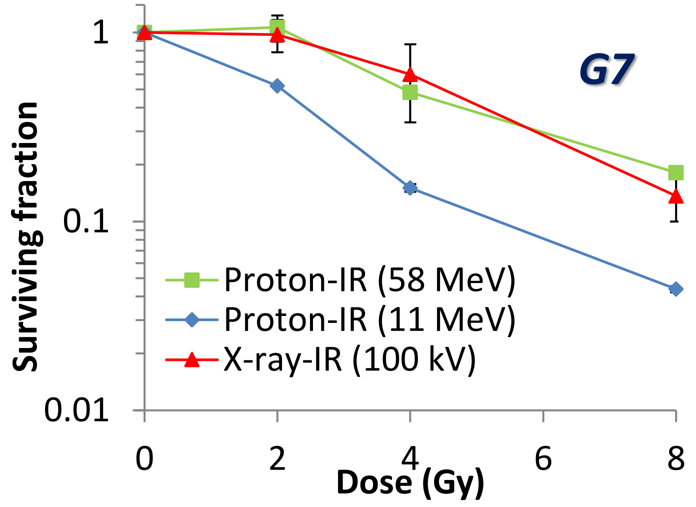
*p<0.02, **p<0.01, ***p<0.005, ****p<0.001

58 MeV (1 keV/μm); 11 MeV (12 keV/μm)

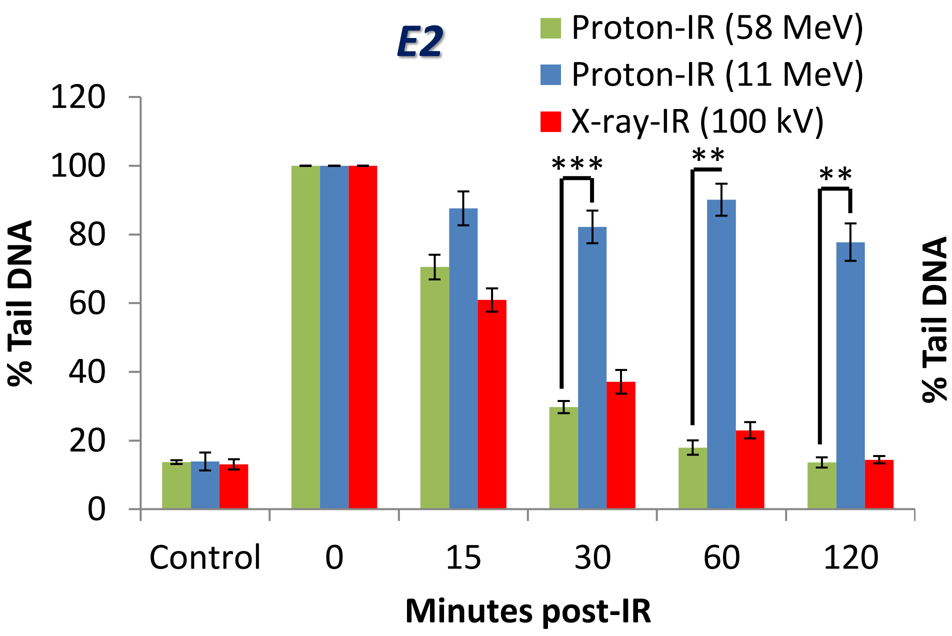
Carter *et al.*, (2018) *Int J Rad Oncol Biol Phys*
Fabbrizi *et al.*, (2021) *Methods Protoc*

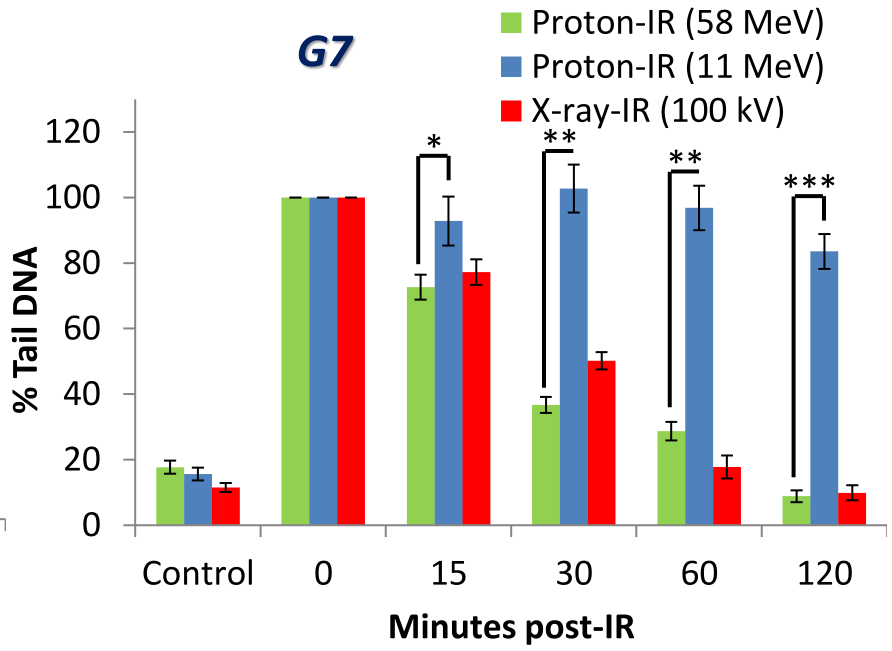
“Relatively” high-LET protons cause a decrease in GBM cell survival due to CDD formation compared to low-LET protons





Alkaline (SSB)

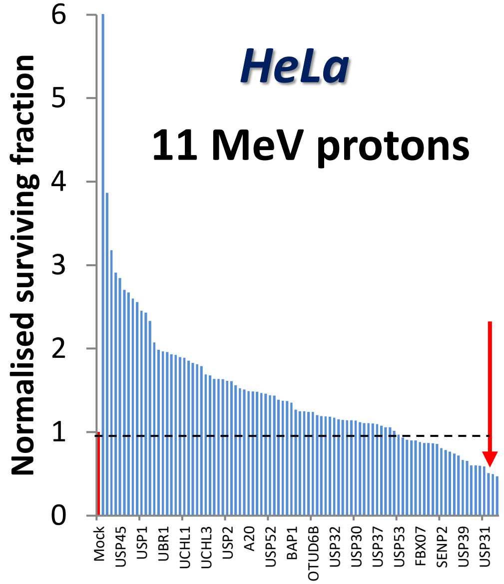


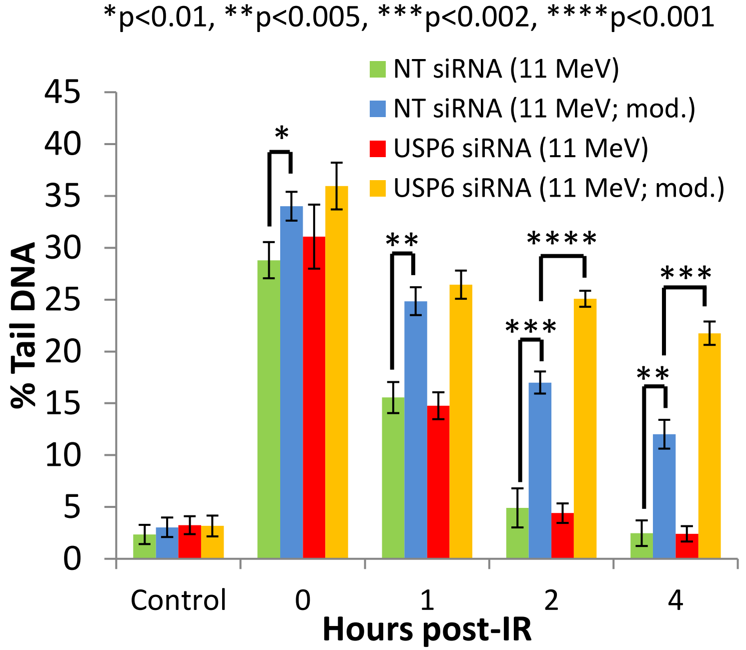


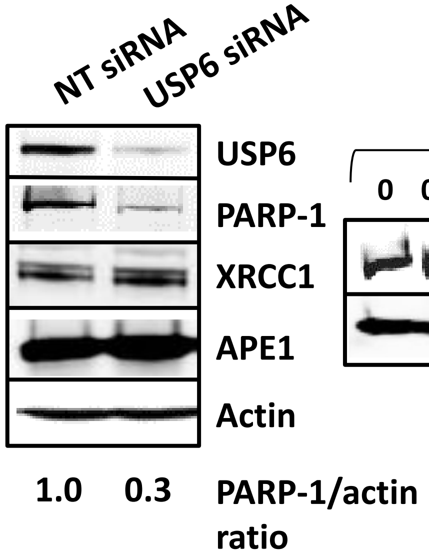
*p<0.02, **p<0.005, ***p<0.002

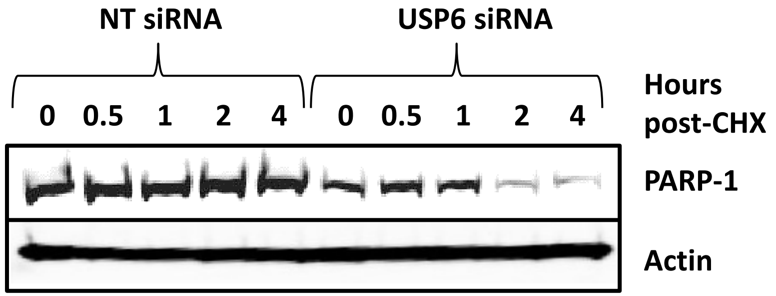
Aiyappa-Maudsley, Chalmers *et al.*, *(Unpublished)*

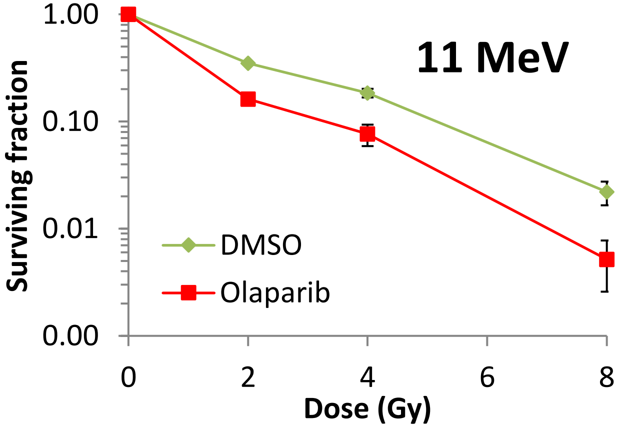
Modulation of proton-induced cellular sensitivity following DUB siRNA knockdown

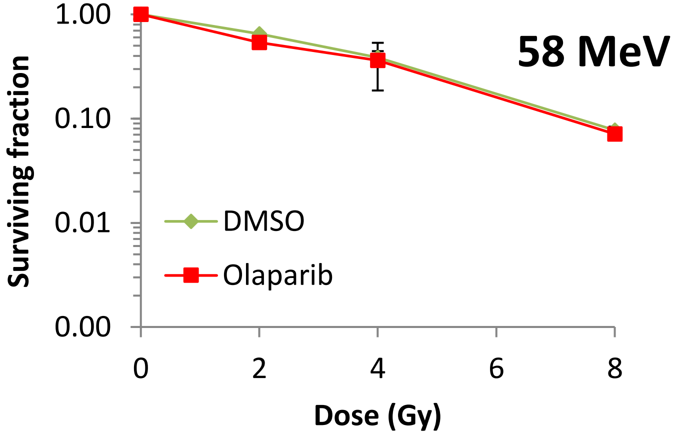


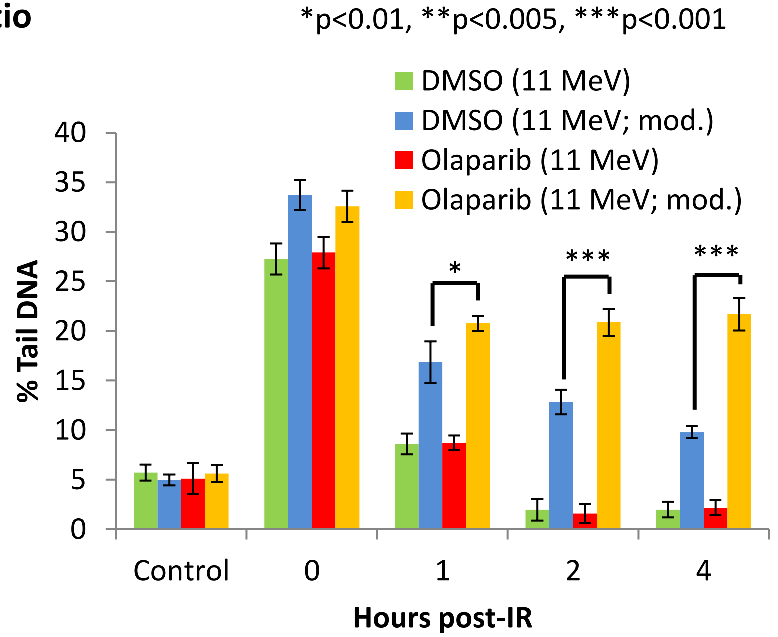






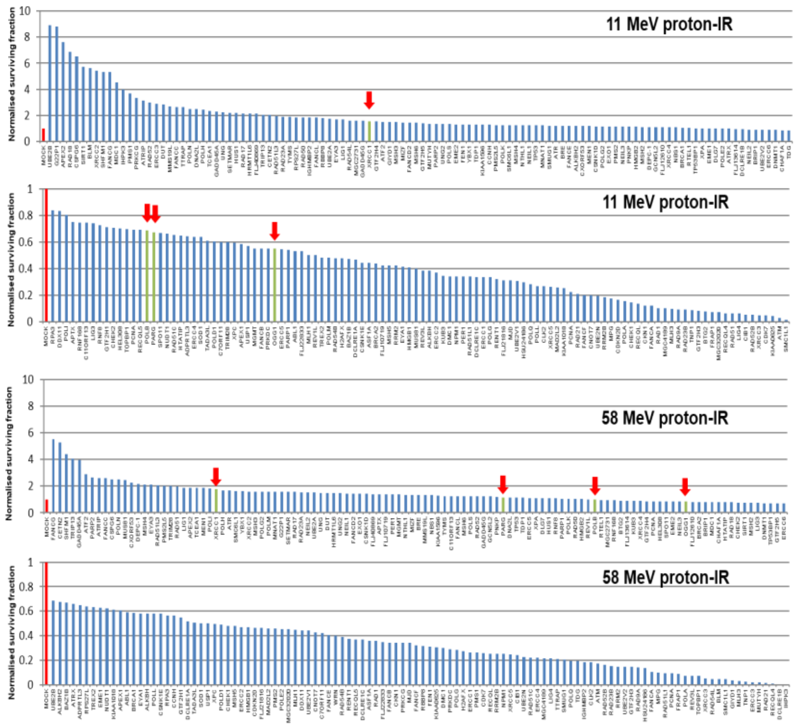


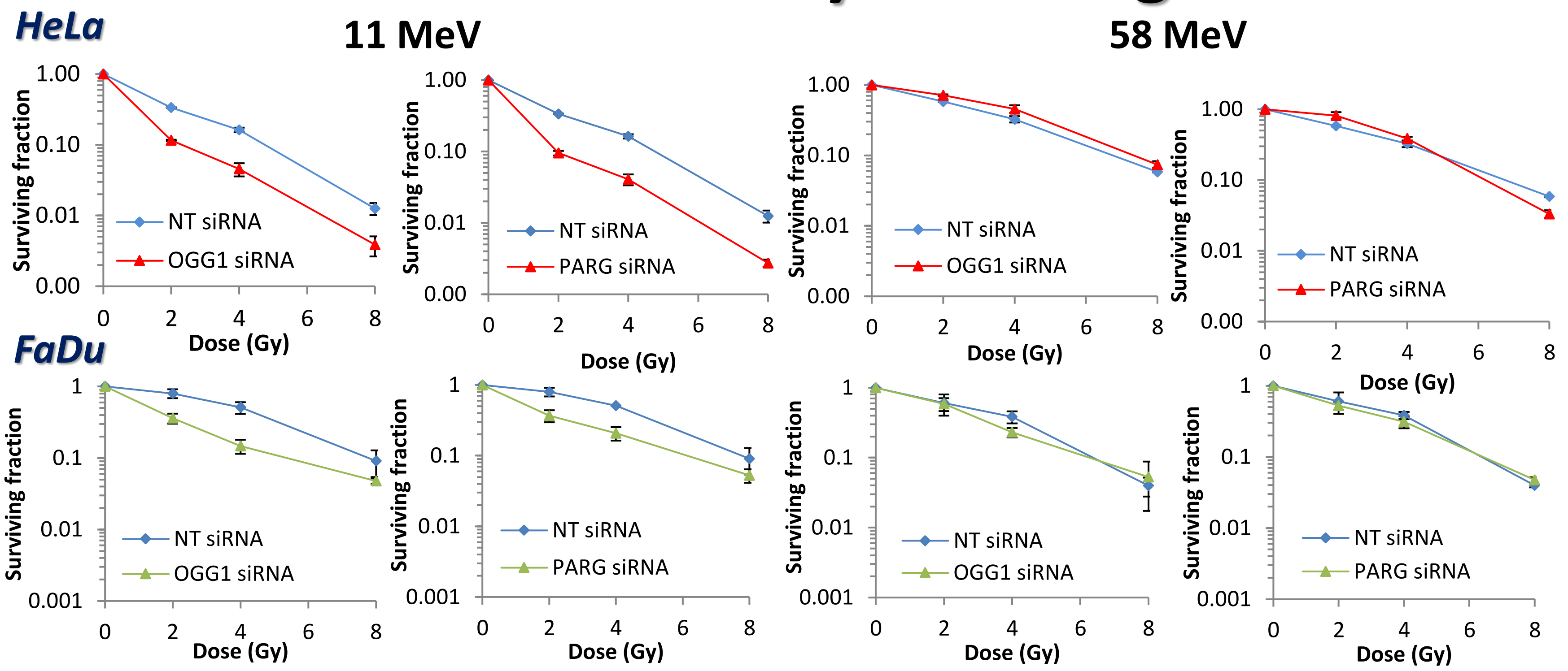


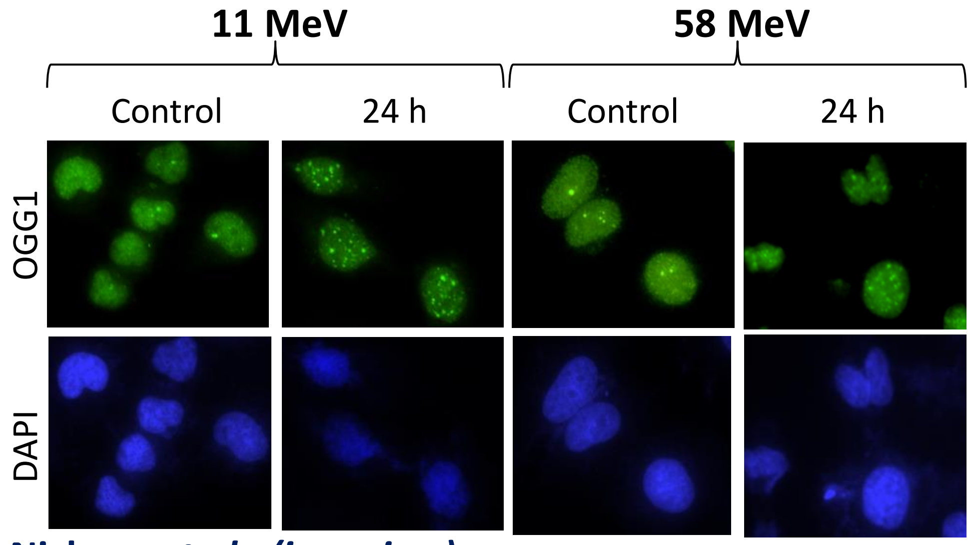


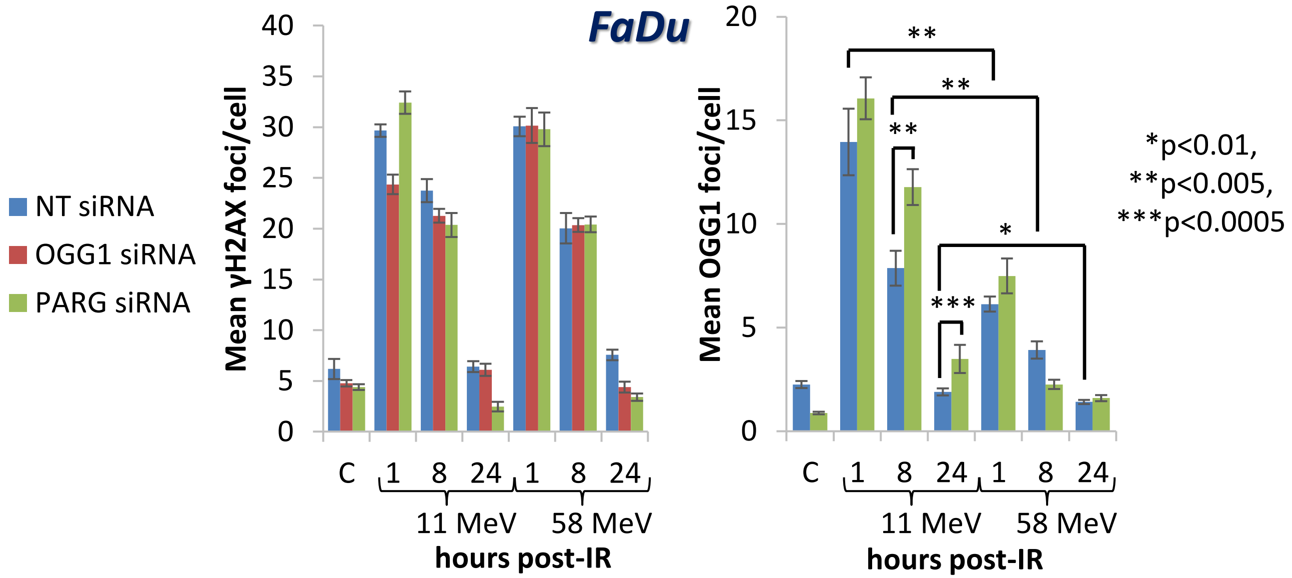
Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*
Nickson, Fabbrizi *et al.*, (2021) *Front Oncol*

Modulation of proton-induced cellular sensitivity following DDR siRNA



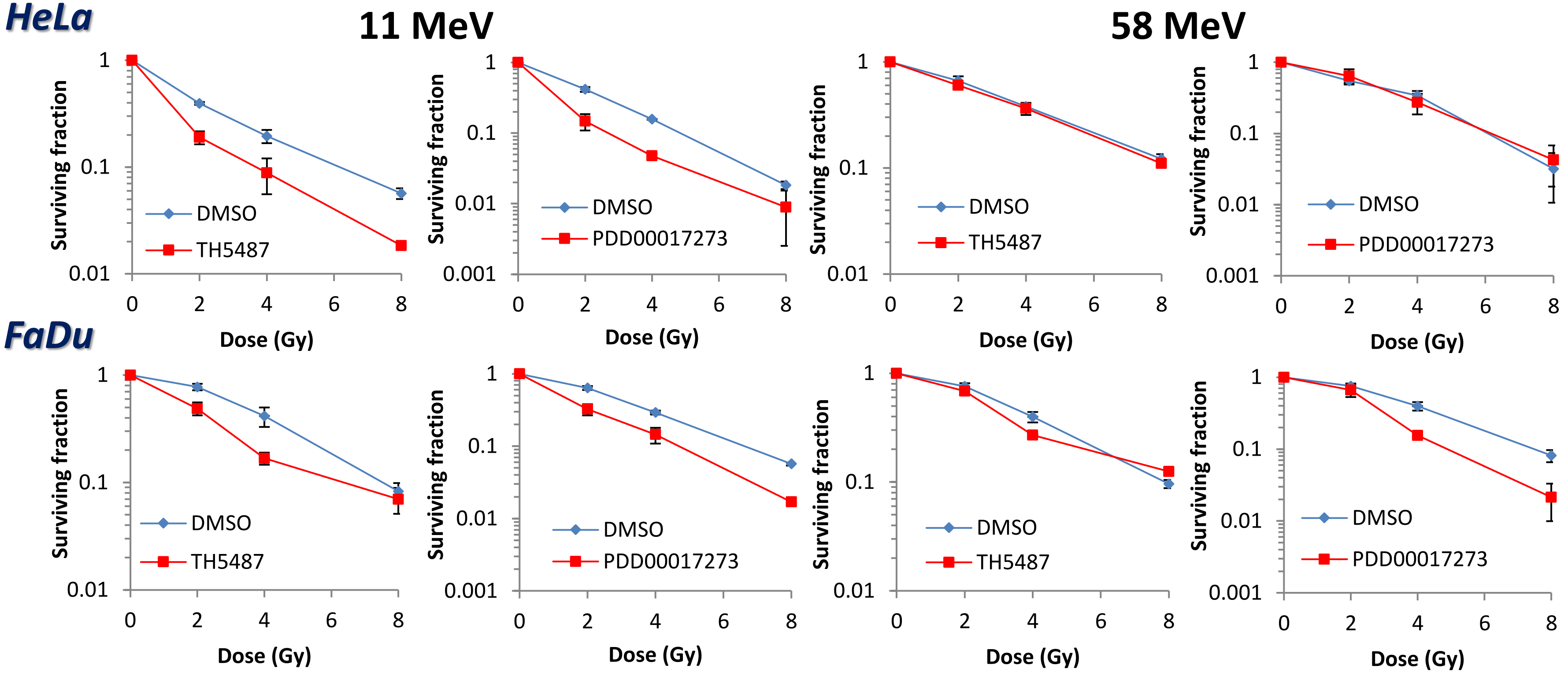


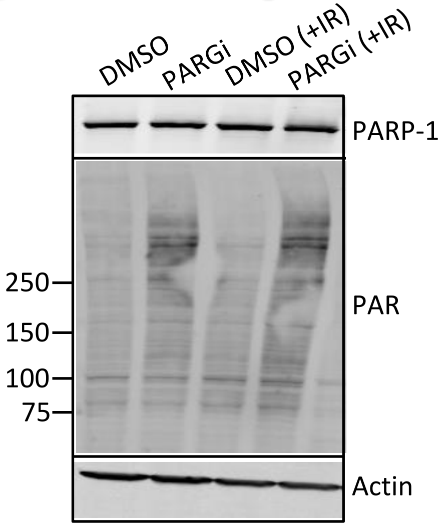


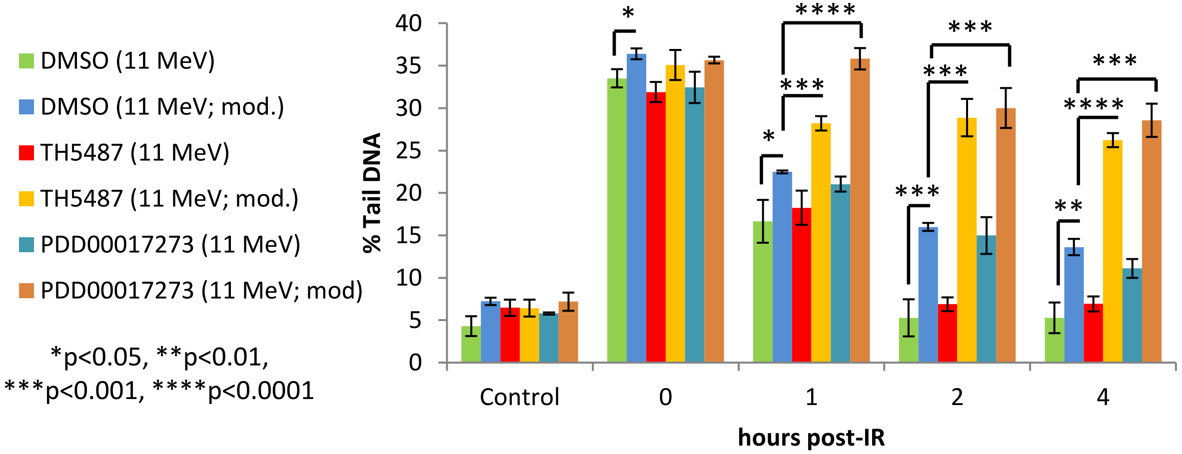


Fabbrizi, Nickson *et al., (in review)*

Targeting OGG1 and PARG sensitises cells to high-LET protons







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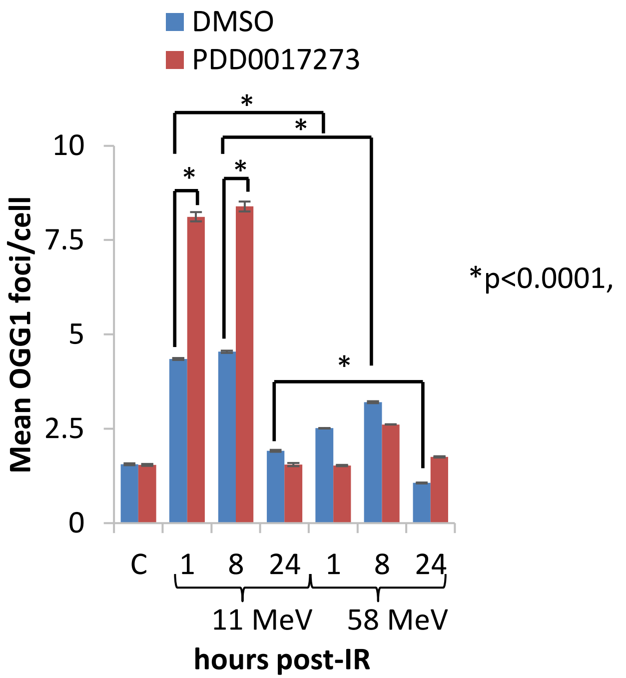

Fabbrizi, Nickson *et al., (in review)*

Collaborations with Thomas Helleday and Helen Bryant

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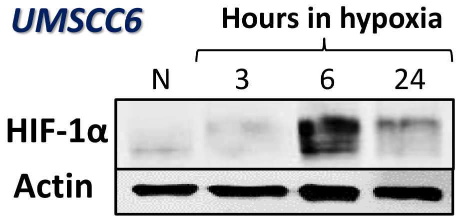
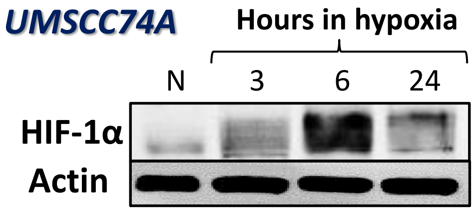
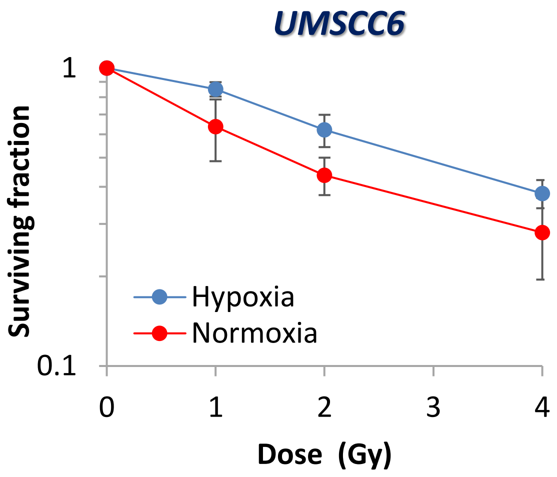
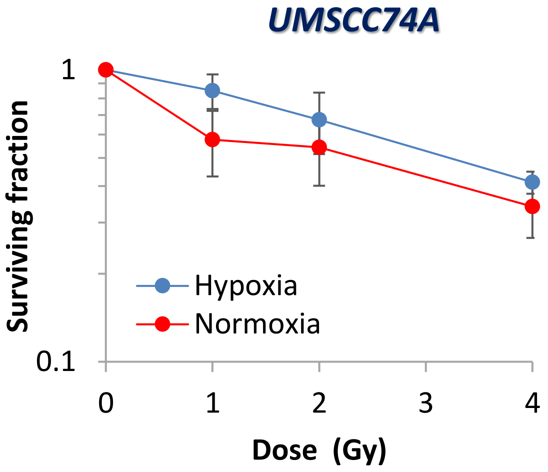
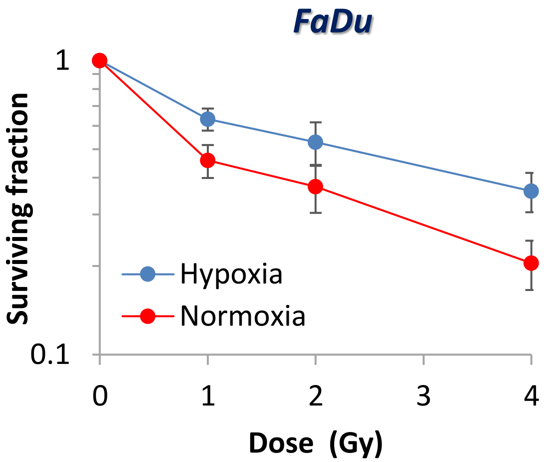
Hypoxia-induced radioresistance and identifying strategies to overcome this using high-LET radiation

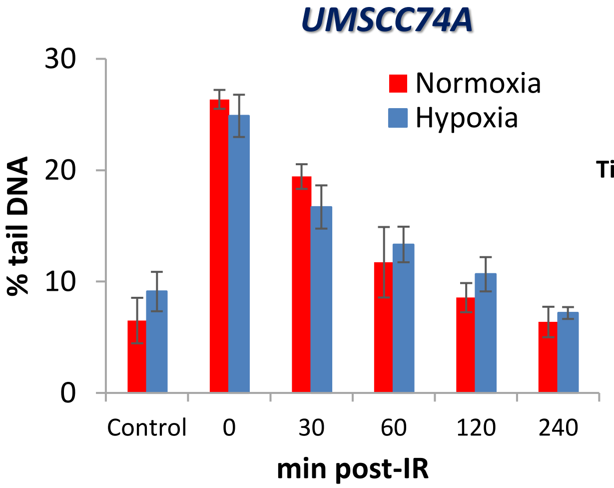


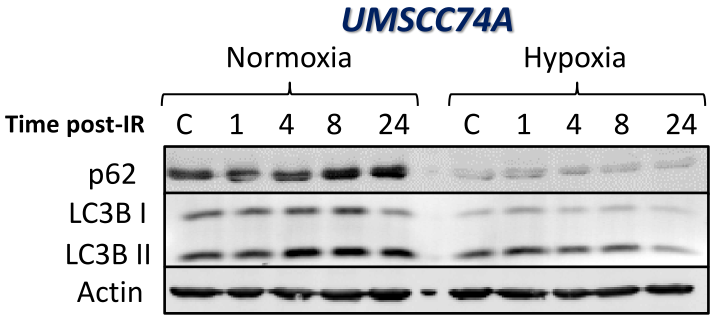


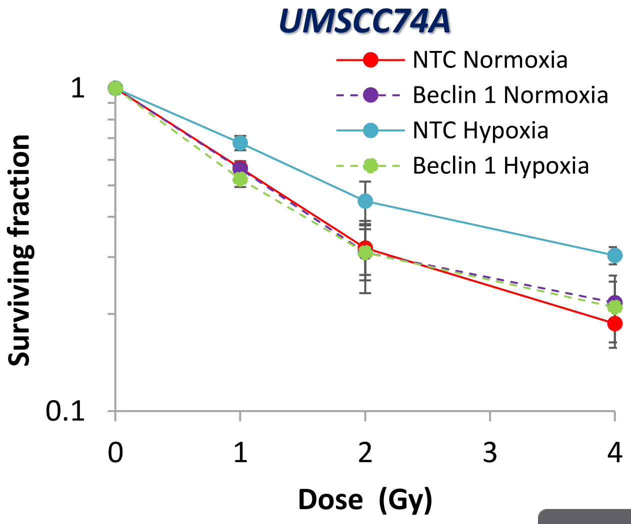


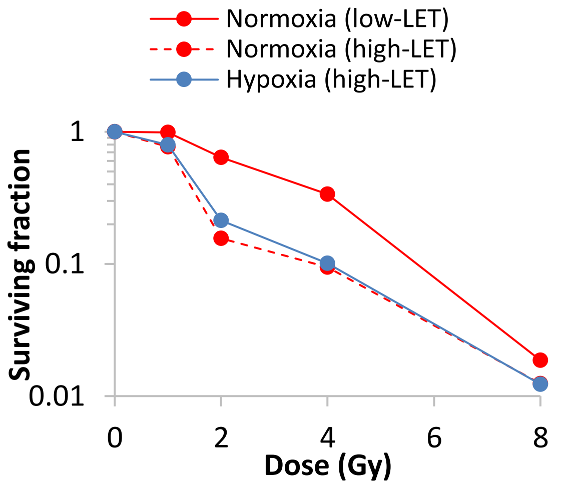












Hill, Rocha *et al., (in review)*

R01CA256854-01

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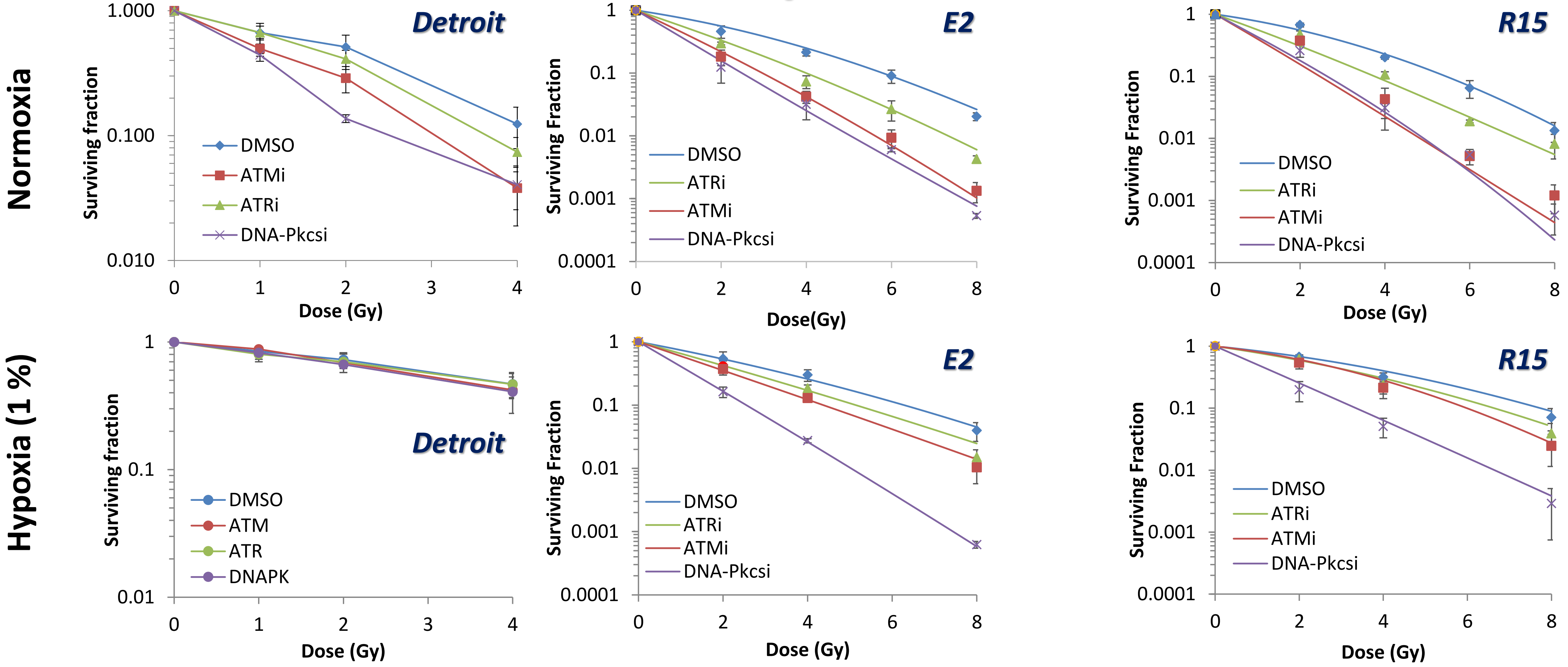
DDR inhibitors can sensitise hypoxic GBM, but not HNSCC, cells to photon irradiation

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



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

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Wait for the next talk!

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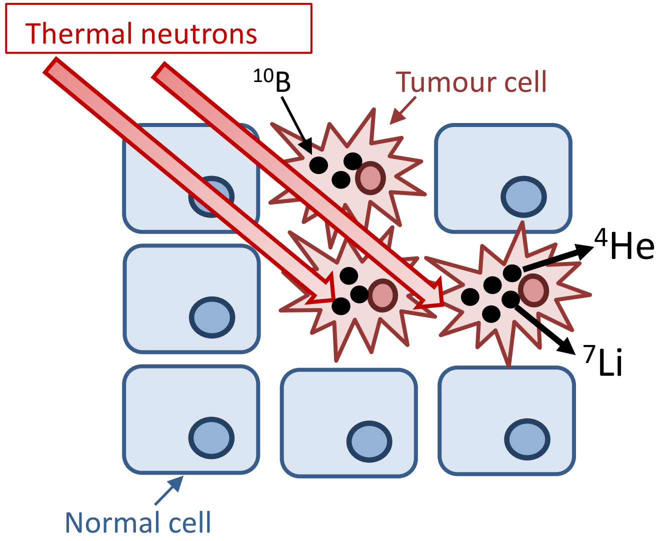
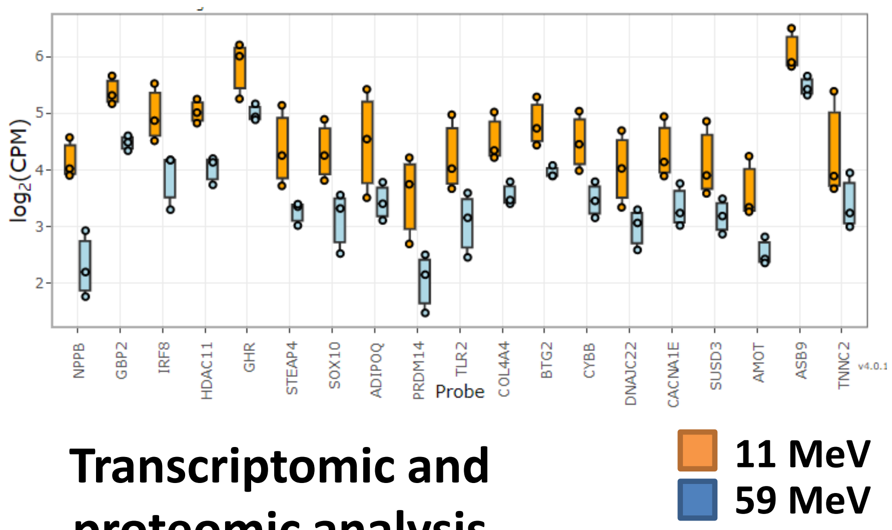
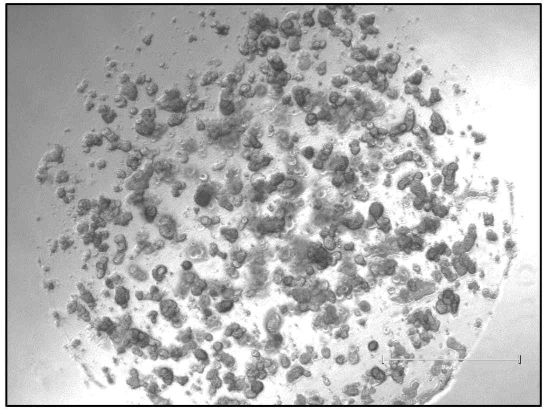
Current radiobiology research focus

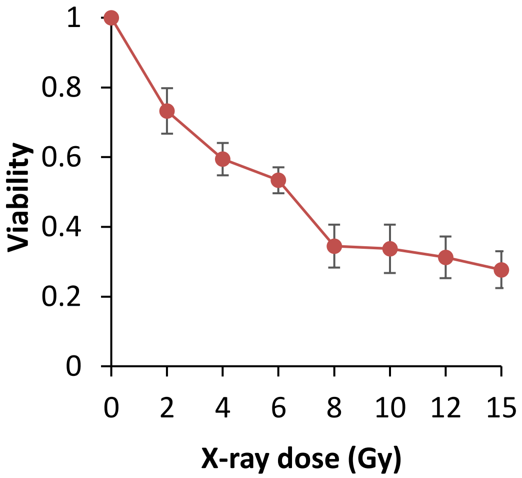


High flux accelerator neutron source for BNCT

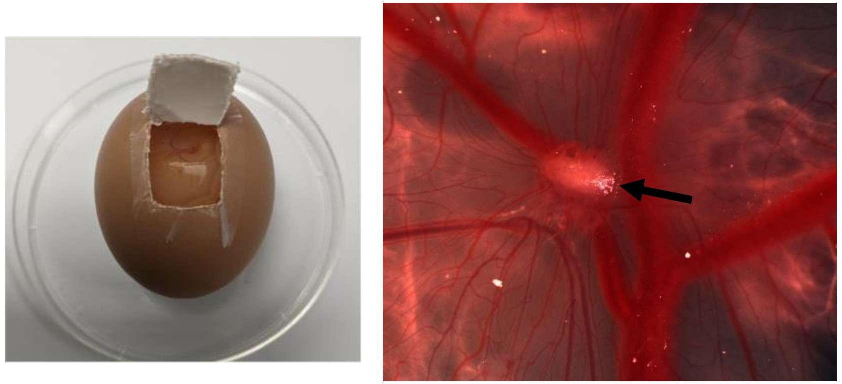


Transcriptomic and proteomic analysis post-irradiation





Development of patient-derived organoids (Inge Tinhofer-Keilholz – Charité Berlin)



Development of chick embryo model

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Summary and key points

- High-LET protons (at Bragg peak distal end), in contrast to low-LET protons, can generate complex DNA complex that contributes to increased cellular radiosensitivity.
- Repair of complex DNA damage induced by high-LET protons is co-ordinated through a specific cellular DNA damage response involving PARP-1, PARG and OGG1.
- Opportunities for exacerbating HNSCC cell killing effects of photons and protons (both low and high-LET) through specific DNA repair inhibitors.
- Other biological factors (hypoxia) and physical factors (dose rate/FLASH) require further investigation.

Acknowledgements

Parsons Group

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

NHS
The Clatterbridge Cancer Centre
NHS Foundation Trust