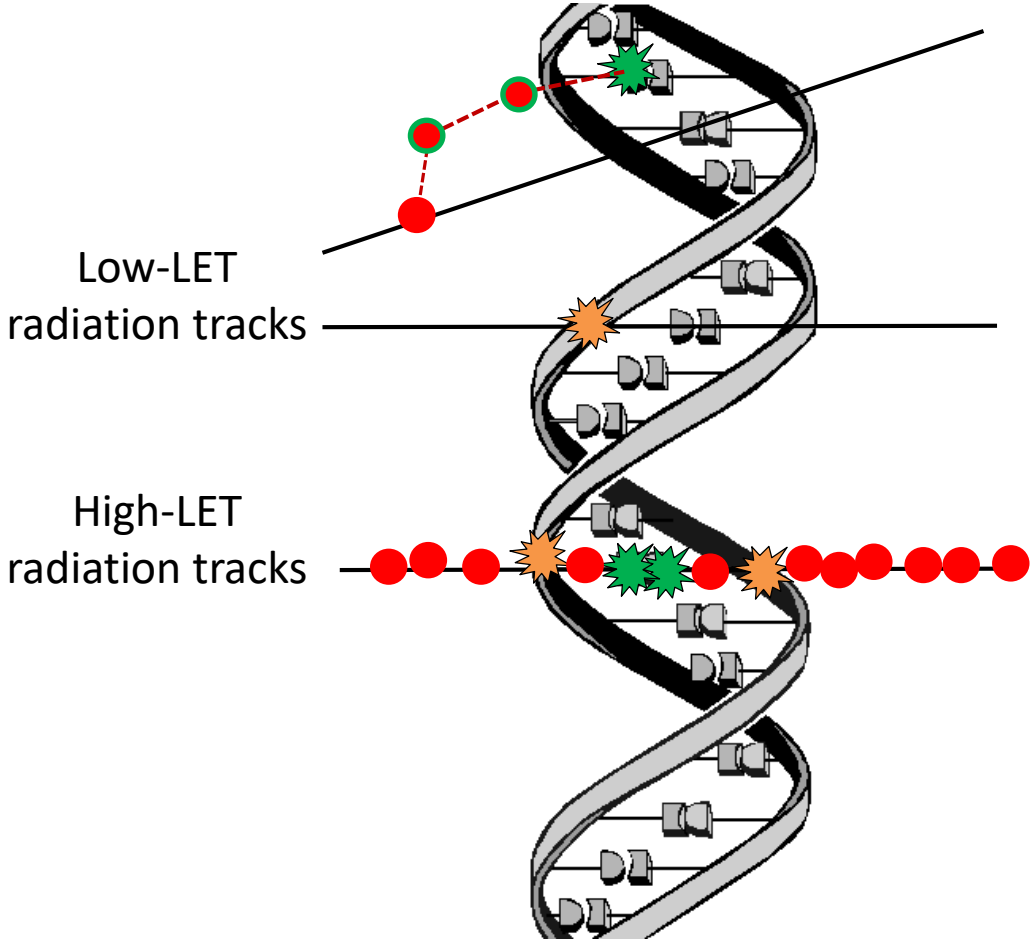
The radiobiology of protons and high-LET particles: Opportunities with LhARA

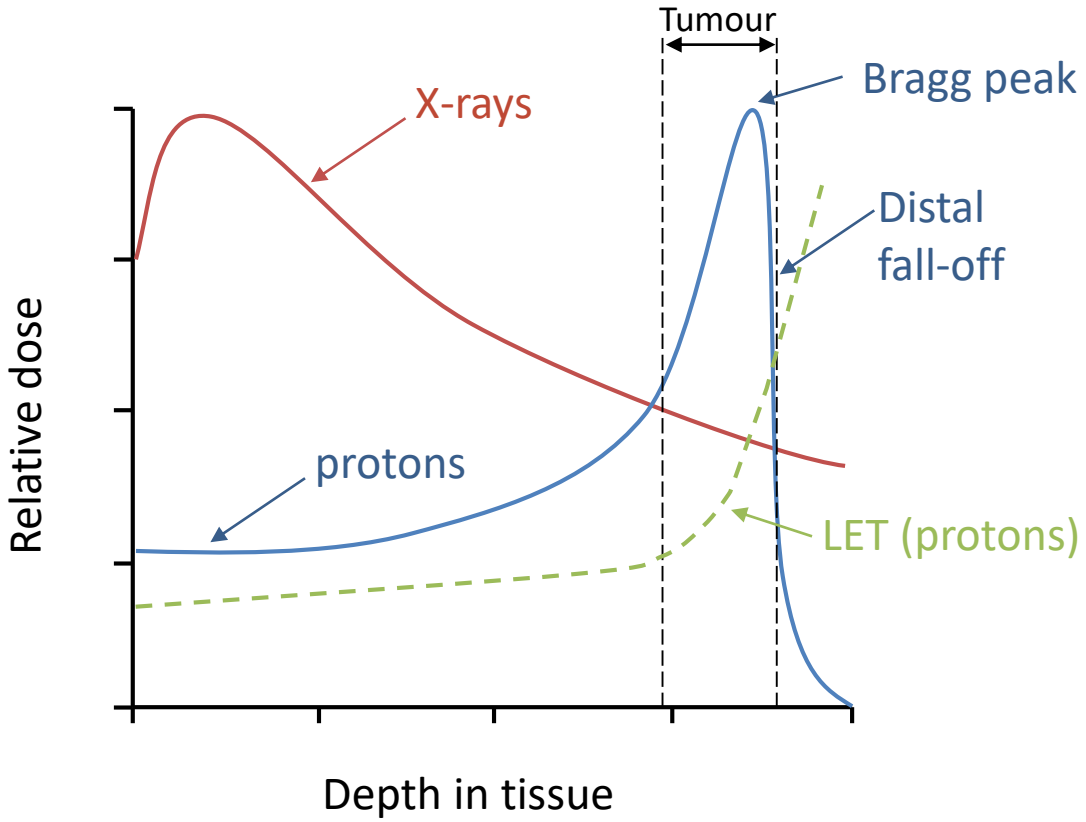
Dr Jason Parsons
Cancer Research Centre
Department of Molecular and Clinical Cancer Medicine

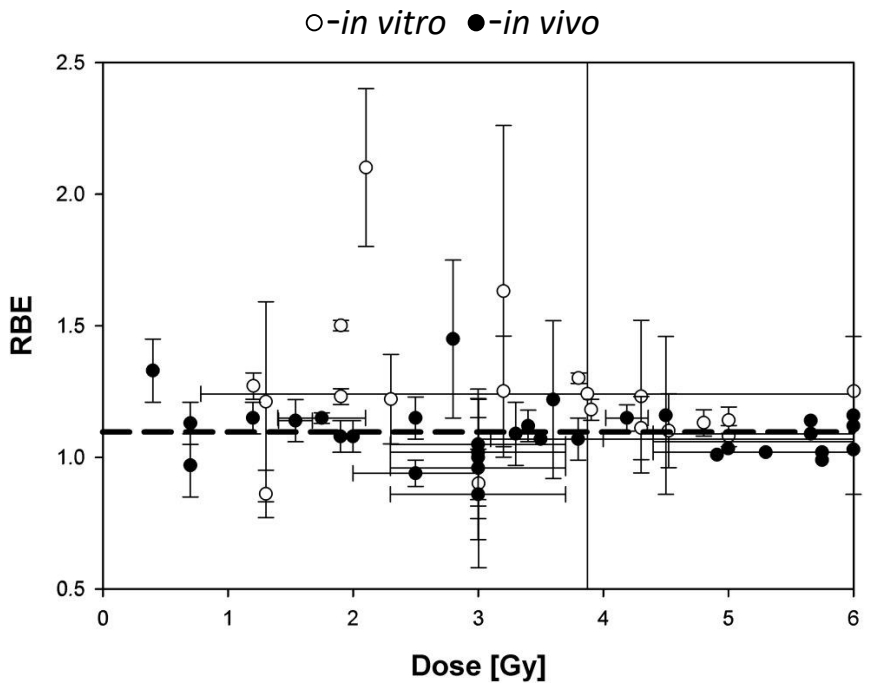
General concepts of radiation biology



- Radiation biology is the study of the action of ionising radiation (IR) on living organisms.
- IR includes electromagnetic radiation (x-rays and γ-rays) as well as charged particles (electrons, protons and heavy ions).
- Linear energy transfer (LET) is the amount of energy transferred per unit length. Low-LET radiation includes x-rays/γ-rays, whereas heavy ions are high-LET.
- Relative biological effectiveness (RBE) is the ratio of the effectiveness of one type of IR compared to another (e.g. x-rays vs heavy ions).

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



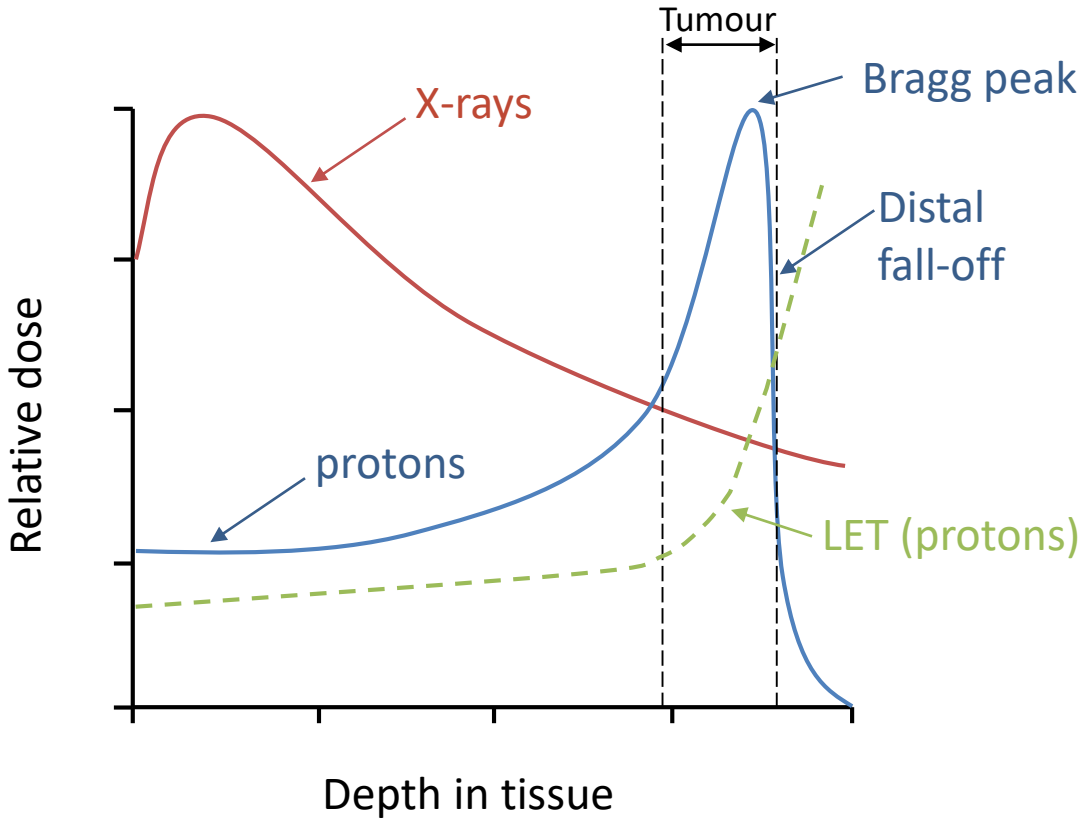


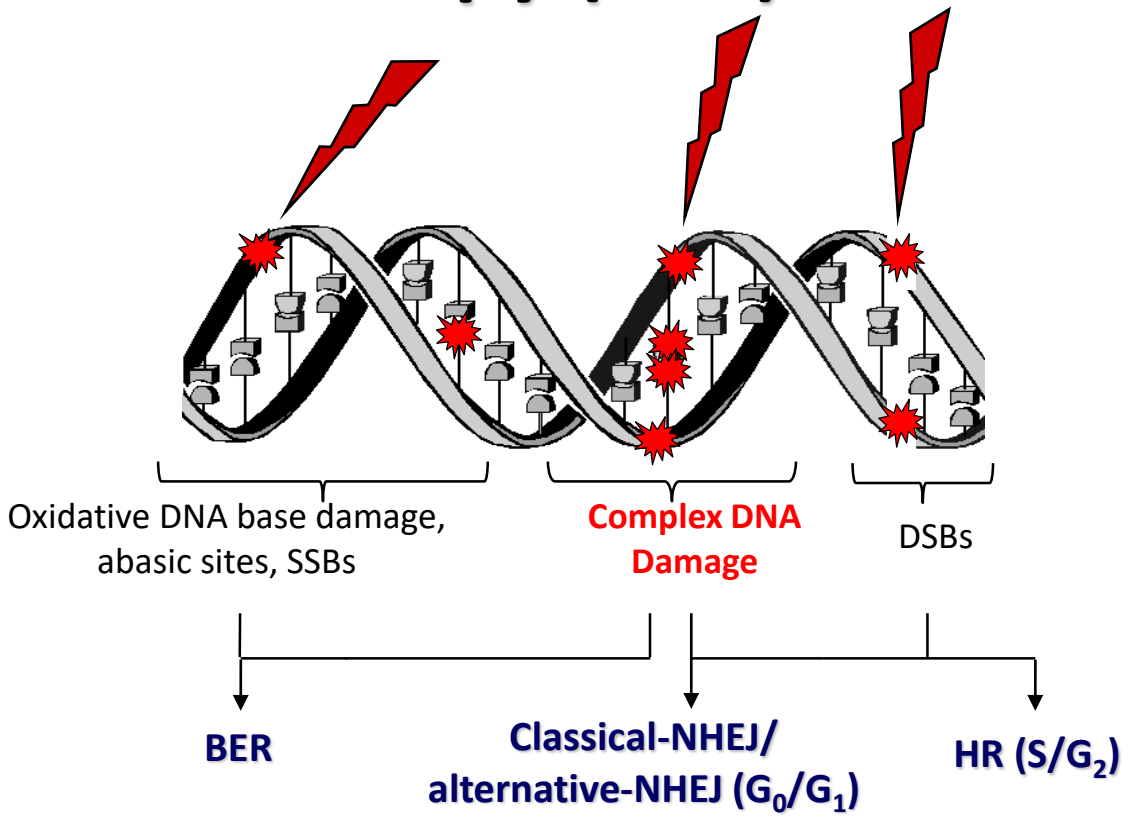
Taken from Paganetti and van Luijk (2013) Sem Rad Oncol

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

Vitti and Parsons (2019) *Cancers*

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



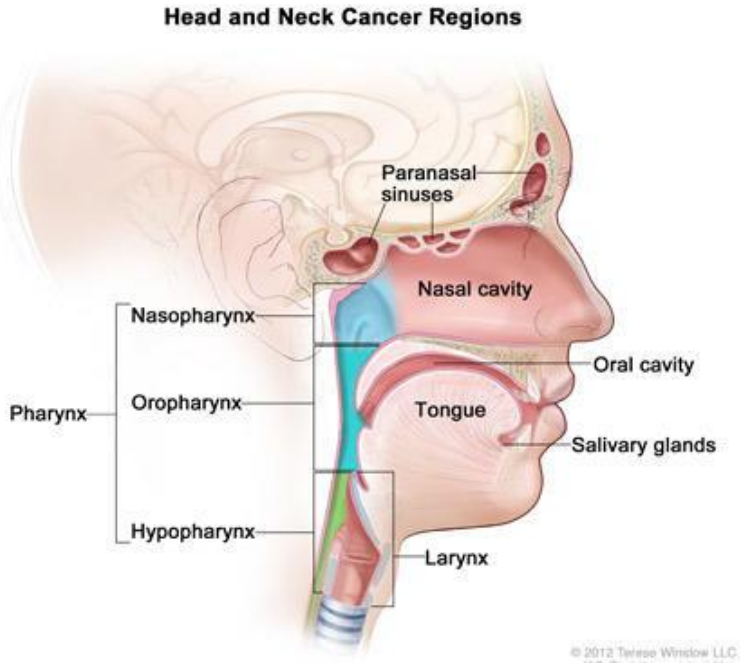


- **Further research exploiting the biological impact of PBT is vital for establishing RBE and optimal clinical treatment for tumours.**

Vitti and Parsons (2019) *Cancers*

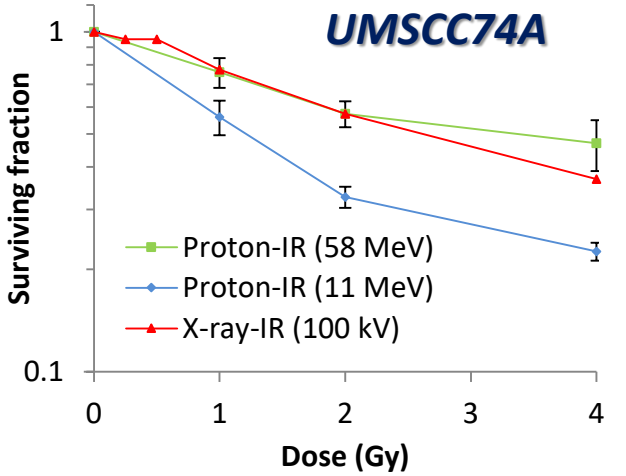
Head and neck squamous cell carcinoma (HNSCC)

- 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).
- E6 and E7 oncogenes cause degradation of p53 and Rb tumour suppressor proteins
- HPV-positive tumours are more sensitive to radiotherapy and chemotherapy, thus improved prognosis, than HPV-negative tumours.

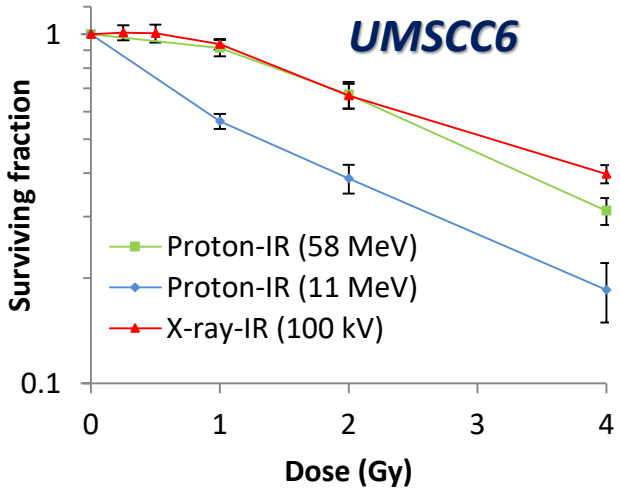


Zhou and Parsons (2020) ***Expert Rev Mol Med***

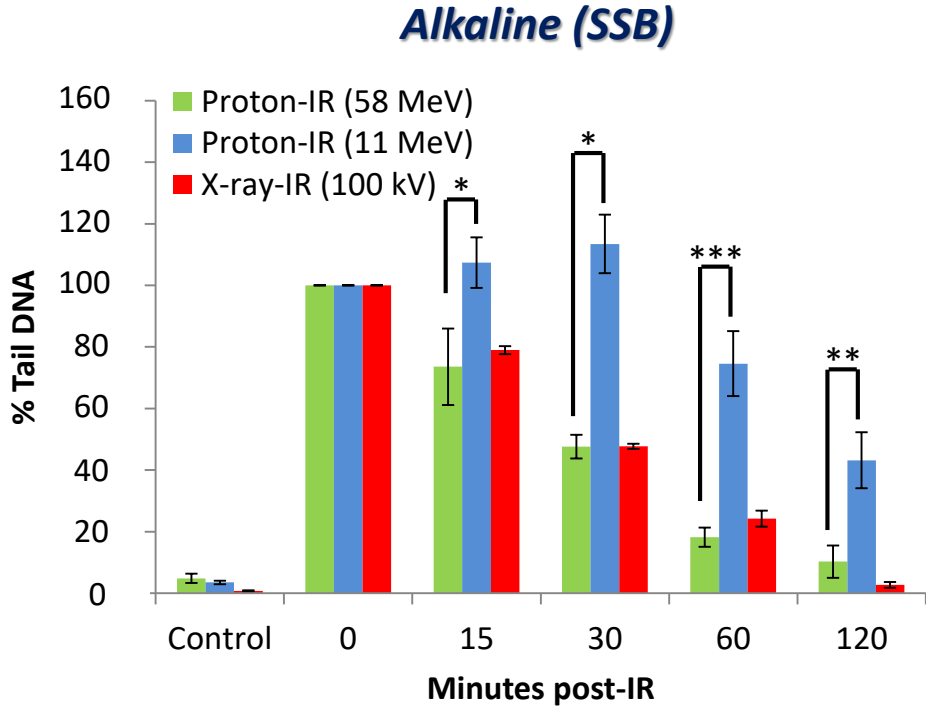
“Relatively” high-LET protons cause a decrease in cell survival due to CDD formation compared to low-LET protons



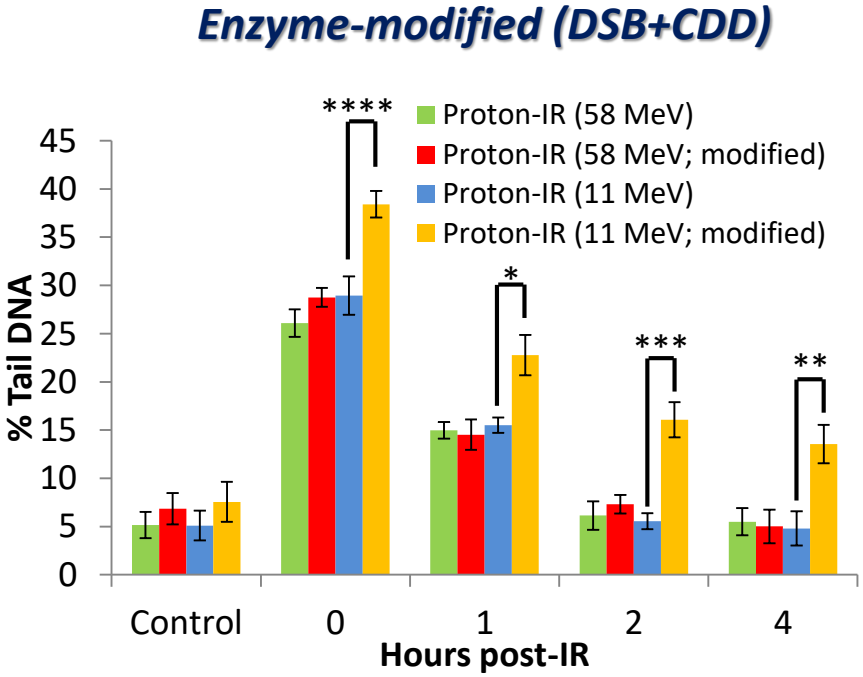
SF2, p<0.02; RBE=1.7



SF2, p<0.01; RBE=1.9



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



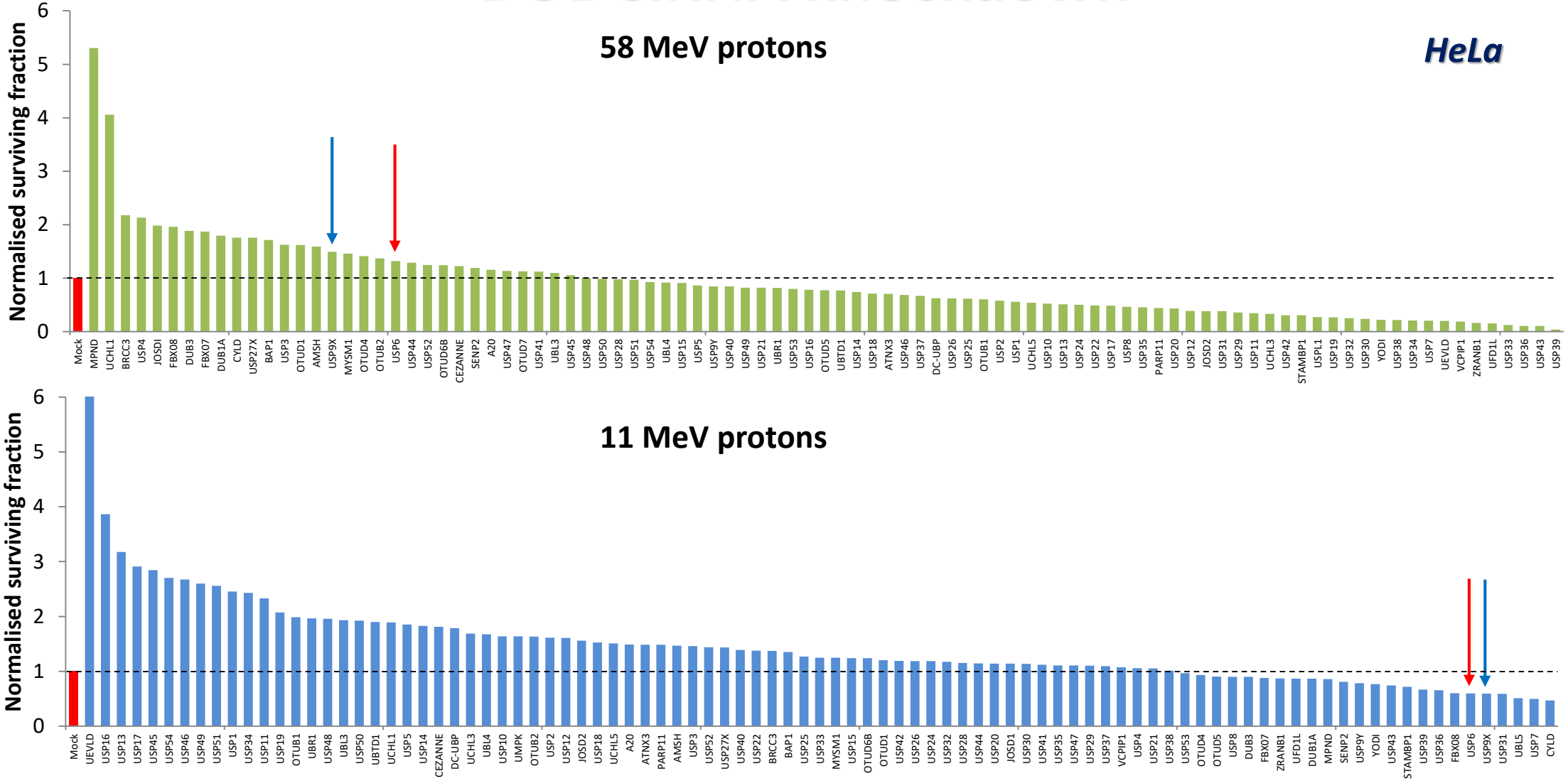
*p<0.02, **p<0.01, ***p<0.005, ****p<0.001

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*

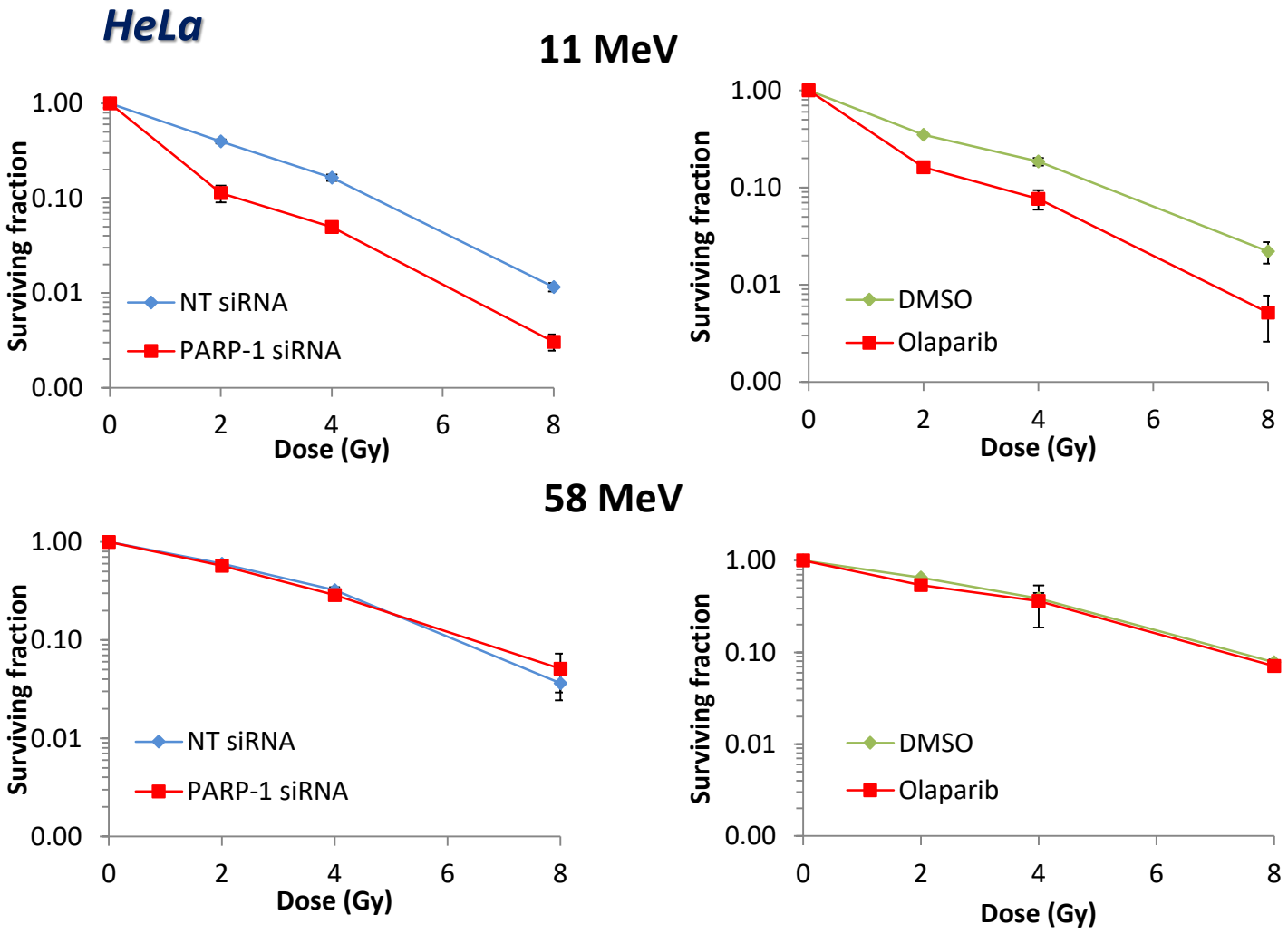
Modulation of proton-induced cellular sensitivity following DUB siRNA knockdown

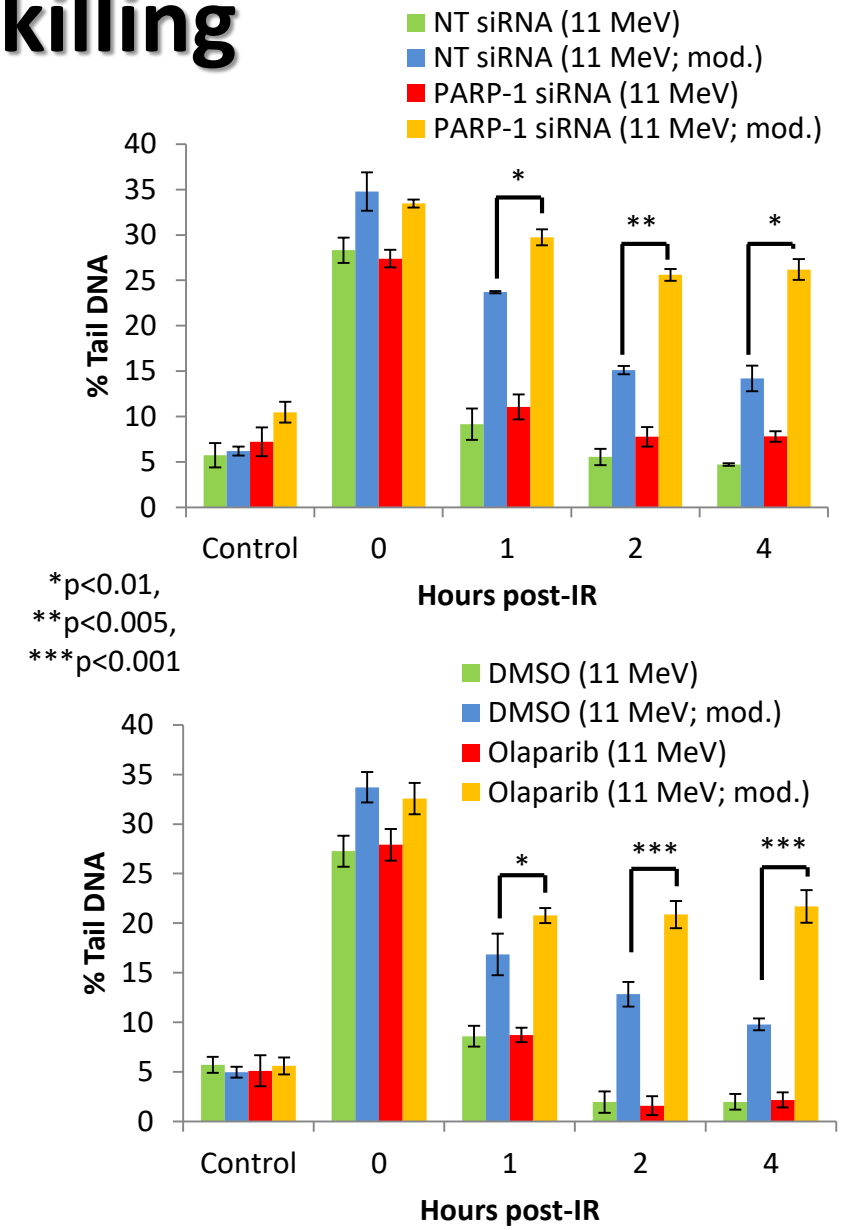


Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*

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

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

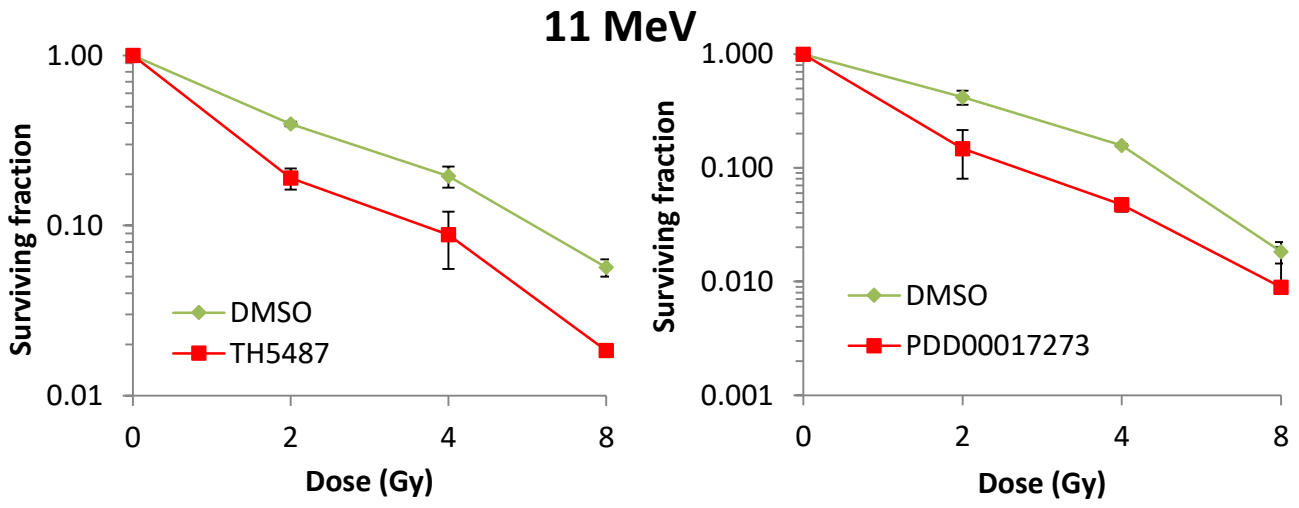


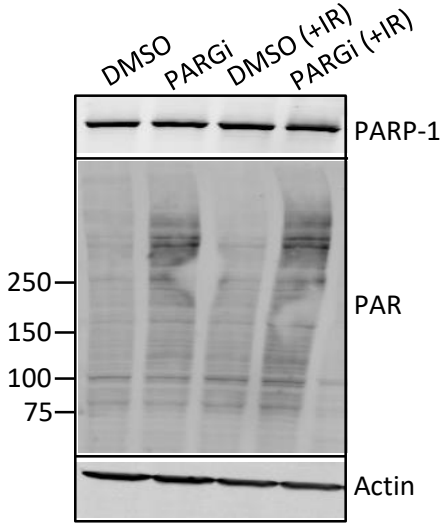


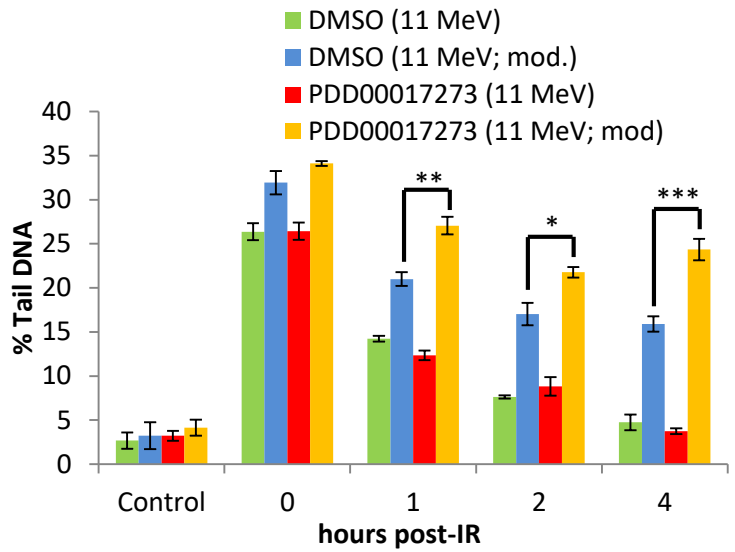
Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*

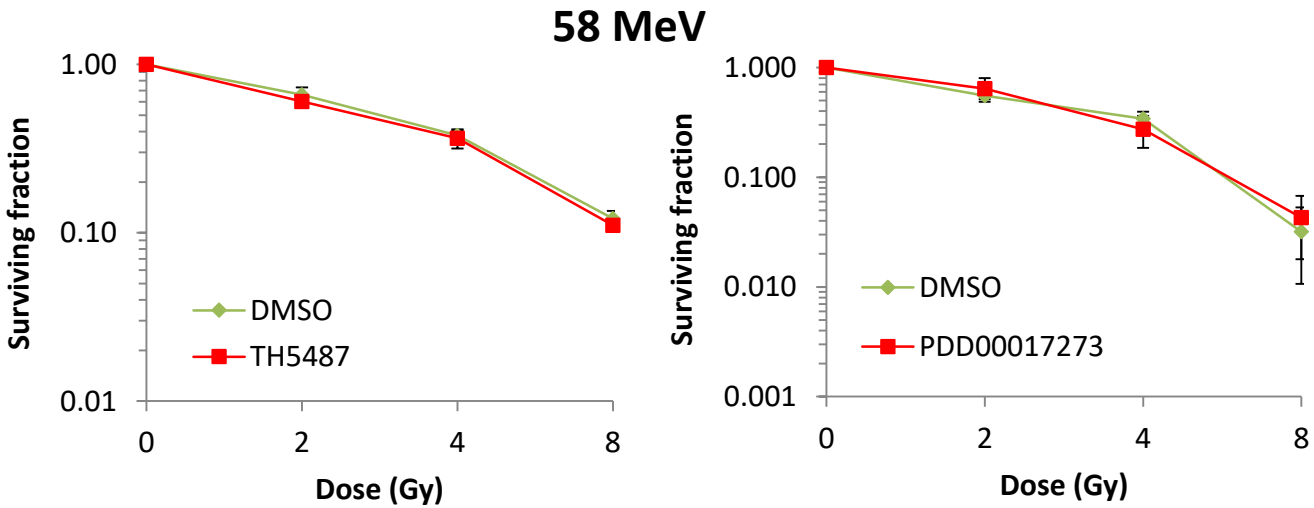
Targeting OGG1 and PARG sensitises cells to high-LET protons

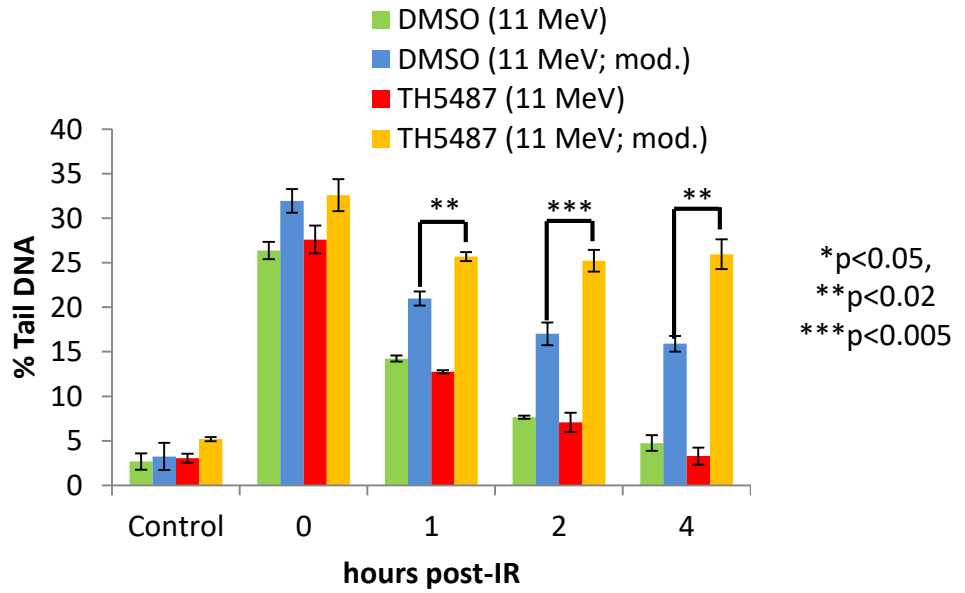
HeLa







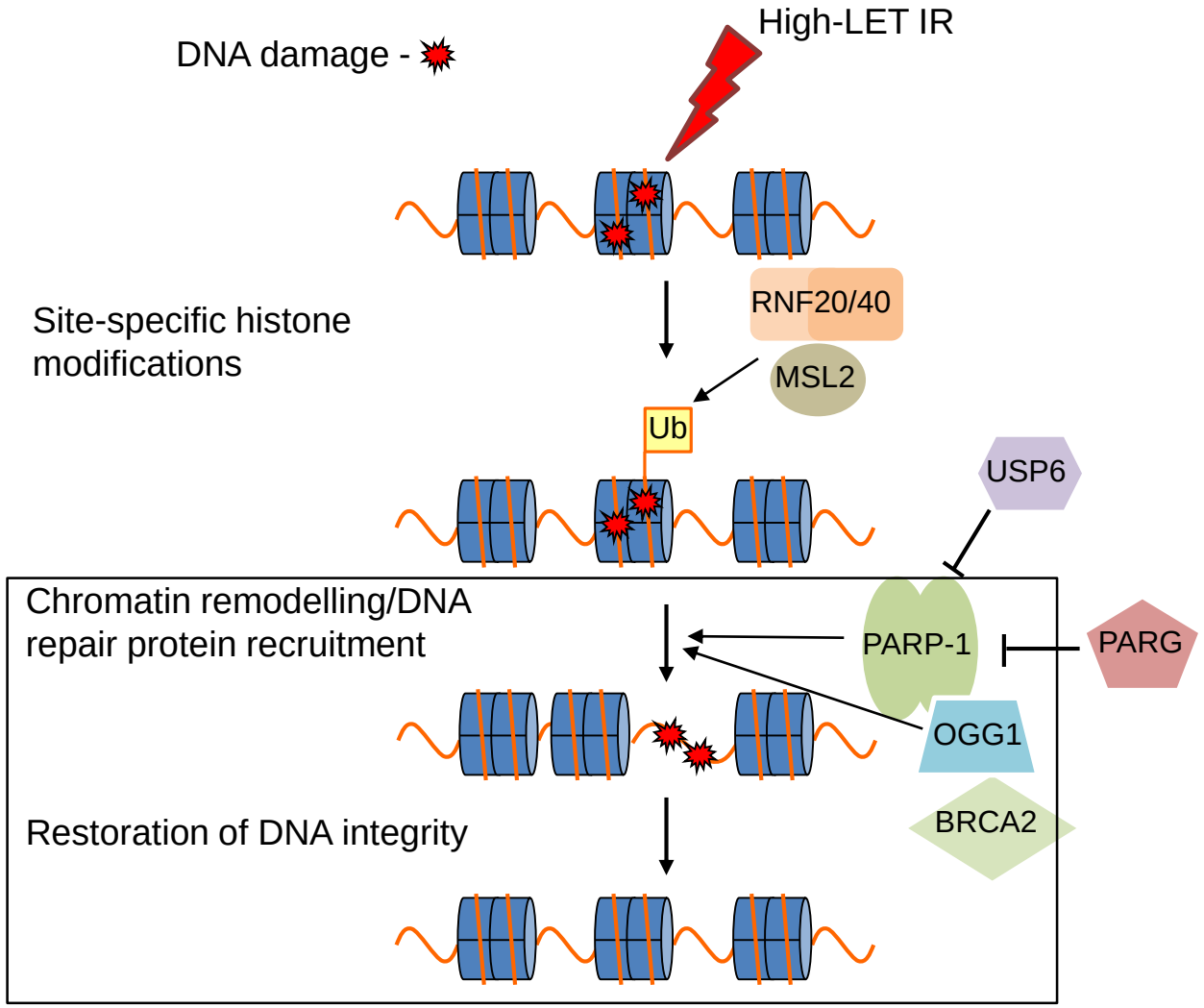




Fabbrizi, Nickson *et al., (unpublished)*

Collaborations with Thomas Helleday and Helen Bryant

Model for the recognition and repair of CDD in chromatin



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)*

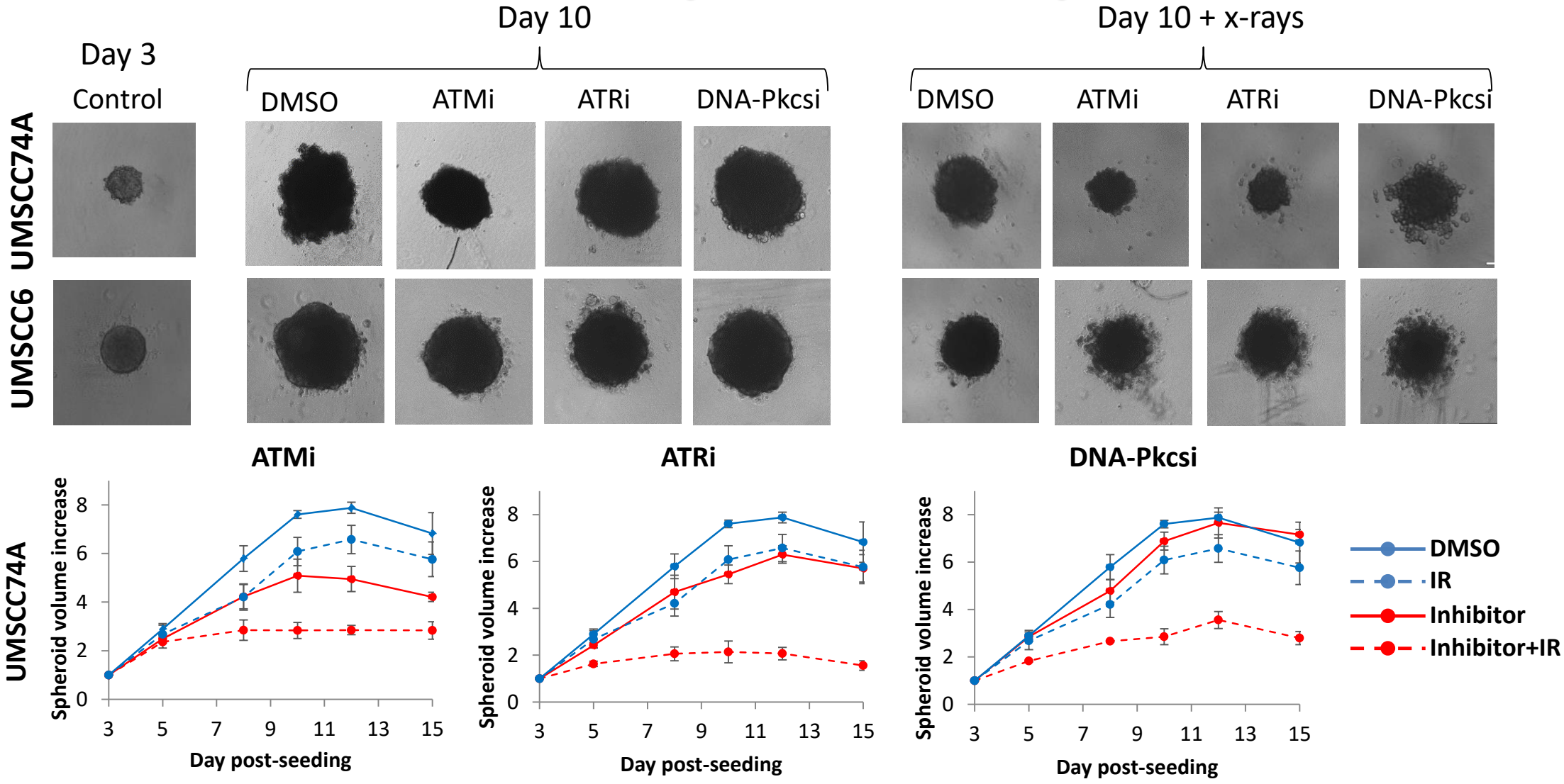
Realizing the radiobiological impact of protons and high-LET particles in head and neck cancer and glioblastoma models

- Multi-Centre award spanning the Universities of Liverpool, Birmingham, Oxford and Glasgow.
- Determine the biological effects of protons and high-LET radiation compared to x-rays on normal versus HNSCC and GBM models, and how this can be optimized for clinical use.

R01CA256854-01

NIH National Institutes of Health
Turning Discovery Into Health

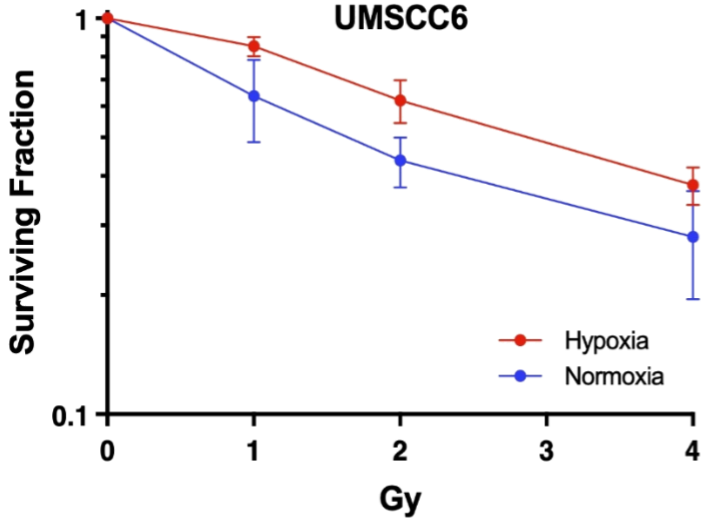
Targeting DNA double strand break repair in 3D models of HNSCC with photons and protons

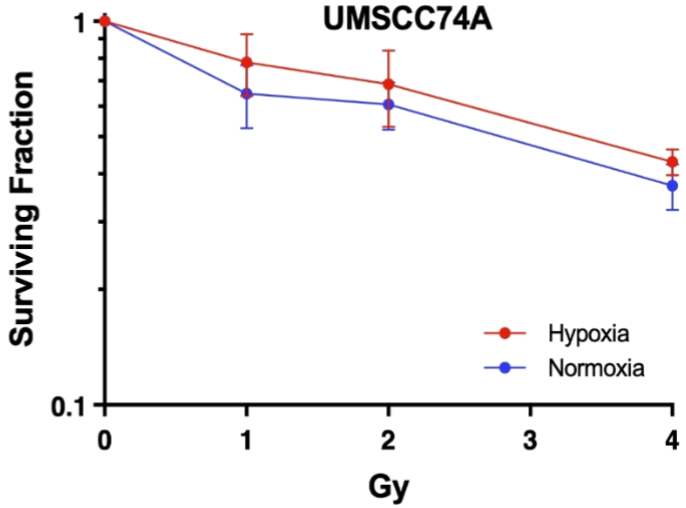


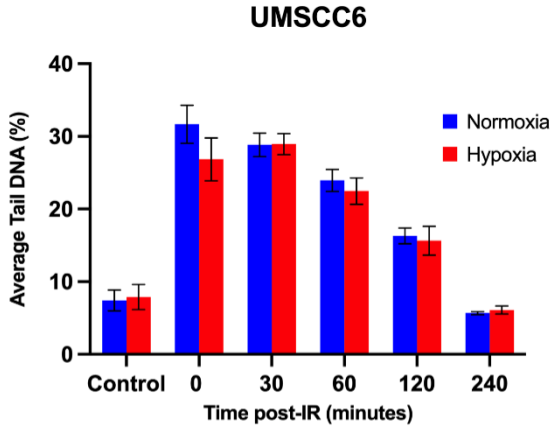
Vitti and Parsons (2020) *Cancers*

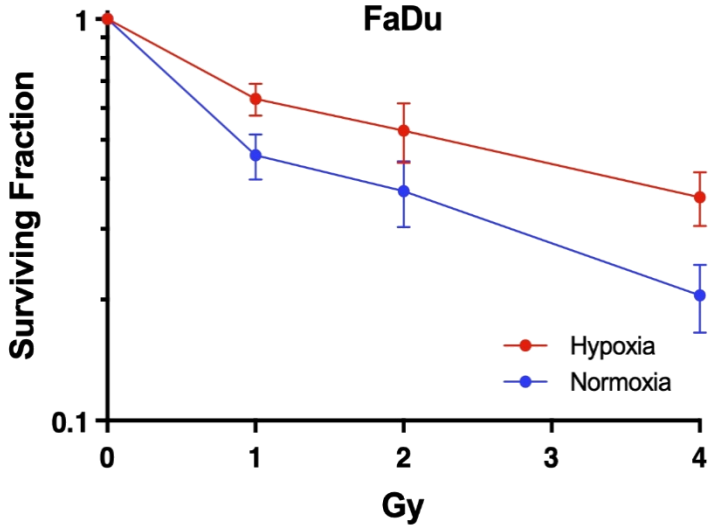
KU-55933 (ATMi); VE-821 (ATRi); KU-57788 (DNA-Pkcsi)

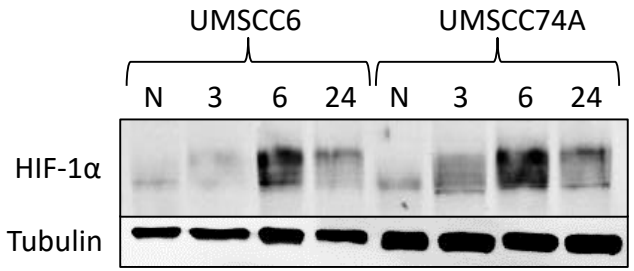
Determine effect of hypoxia on radiobiology, and identify strategies to overcome radioresistance.

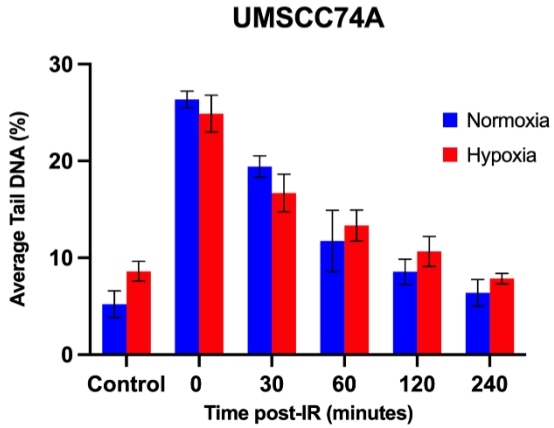








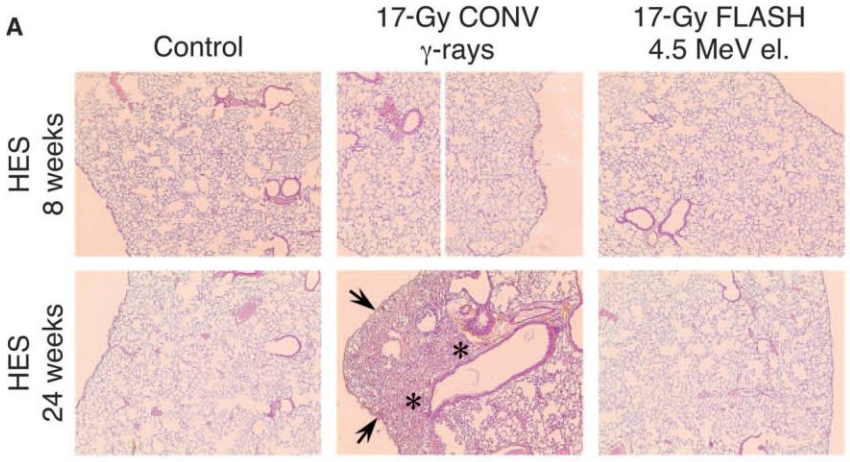




Hill, Frost, Rocha *et al., (Unpublished)*

Examine the radiobiology of FLASH high-LET radiation.

- Using ultra high-dose rates (>40 Gy/s; versus ~5 Gy/min).
- FLASH stimulates normal tissue sparing.



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

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

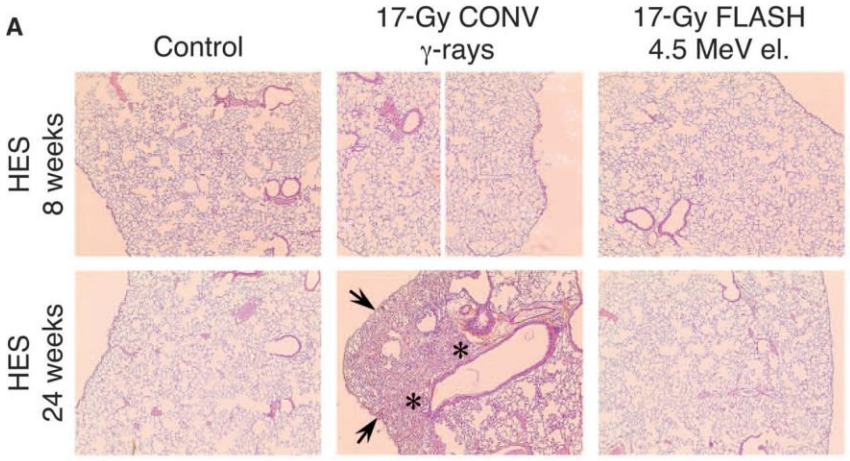
Bourhis *et al* (2019) *Radiother Oncol*

- Little evidence of tumour cell killing effect of FLASH.
- Mechanism of action unclear (prominent role for oxygen?).
- Opportunity for utilisation of FLASH protons/particles.

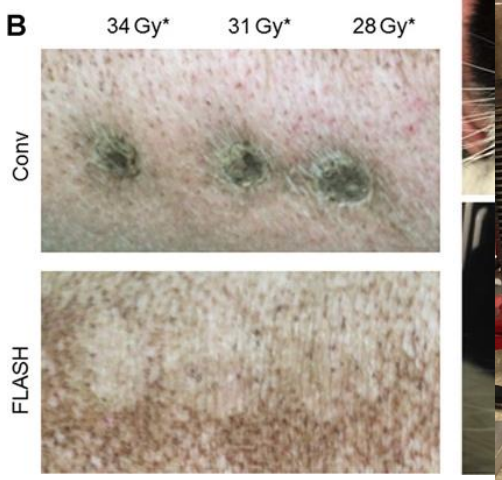
Hughes and Parsons (2020) *Int J Mol Sci*

Examine the radiobiology of FLASH high-LET radiation.

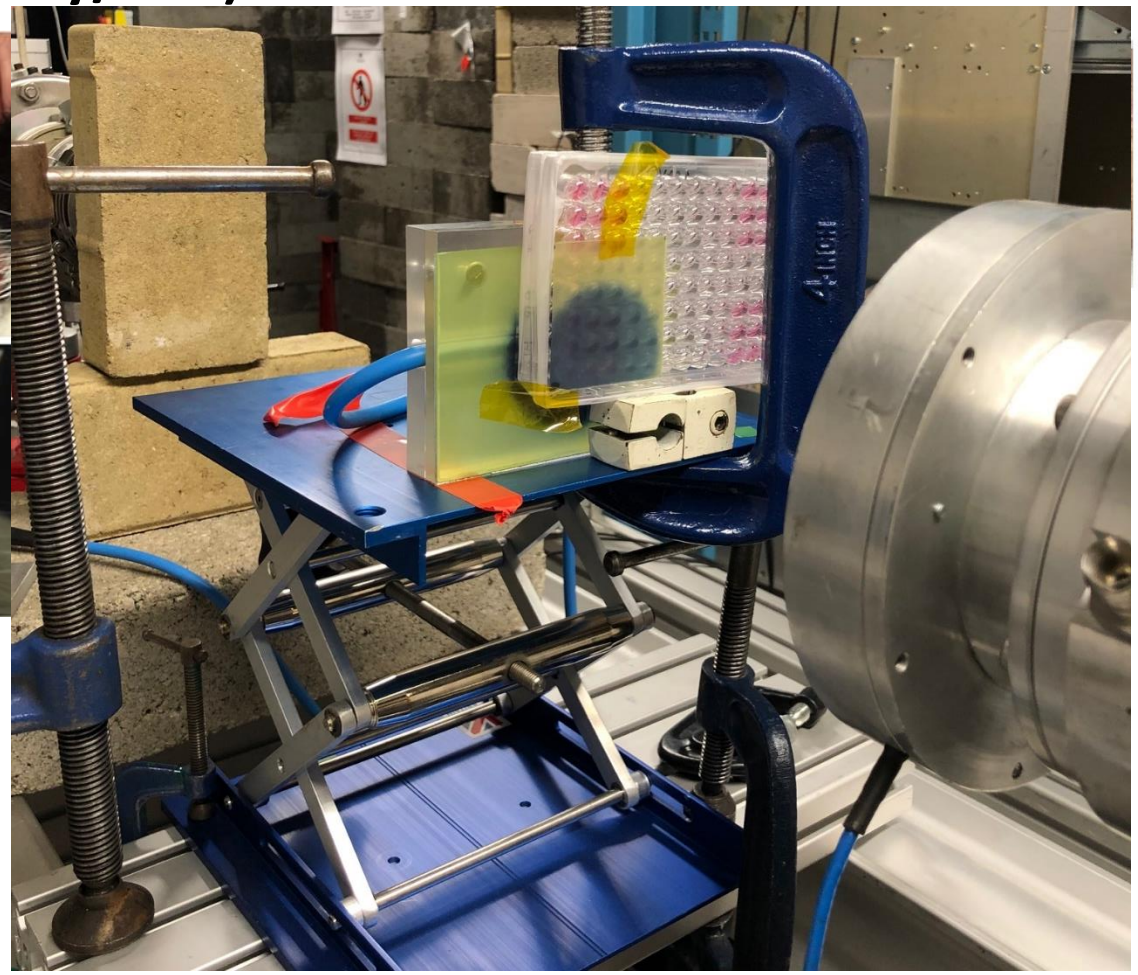
- Using ultra high-dose rates (>40 Gy/s; versus ~5 Gy/min).
- FLASH stimulates normal tissue sparing.



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



Vozenin *et al* (2018)



- Little evidence of tumour cell killing effect of FLASH.
- Mechanism of action unclear (prominent role for oxygen?).
- Opportunity for utilisation of FLASH protons/particles.

Establishment of FLASH protons in Birmingham

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

Collaborations with Stuart Green, Tzany Wheldon and Kristoffer Petersson

Radiobiology Research Working Group Meeting (8th January 2021)

Present:
Jason Parsons (University of Liverpool; Chair)
Ken Long (Imperial College London)
Karen Kirkby (University of Manchester)
Yolanda Presado (Institut Curie)
Amato Giaccia, Mark Hill and Kristoffer Petersson (University of Oxford)
Giuseppe Schettino (National Physics Laboratory/University of Surrey)

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.
- *In vitro* and *in vivo* end-stations both for routine cell culture experiments, but also animal irradiations.
- Stimulate the analysis of more complex biological end-points; potential for live cell imaging.
- Enable clinically-relevant dose fractionation experiments, and combinatorial treatments (e.g. targeted drugs/inhibitors).
- Delivery of ultra high dose rates (FLASH) and the biology behind this phenomenon.
- Unique ability to combine proton minibeam with FLASH.

Acknowledgements






Parsons Group

Rachel Carter
Katie Nickson
Terpsi Vitti

Maria Rita Fabbrizi
Jonathan Hughes
Julianty Frost
Radhika Aiyappa-Maudsley
Beth Wilkinson
Emily Robinson
Chumin Zhou
Rhianna Hill
Jennifer Antrobus
Sifaddin Konis
Aderonke Abah
George Duffield
Emma Melia

Institute of Systems, Molecular and Integrative Biology

Mike Clague, Sylvie Urbe
Sonia Rocha, Terry Jones

Clatterbridge Cancer Centre

Andrzej Kacperek

University of Glasgow

Anthony Chalmers

Oxford Institute for Radiation Oncology

Mark Hill
James Thompson
Kristoffer Petersson

University of Birmingham

Stuart Green
Tzany Wheldon
Ben Phoenix

Imperial College London

Ken Long

AstraZeneca

Stephen Durant
Alan Lau