# LhARA: Summary and Outlook

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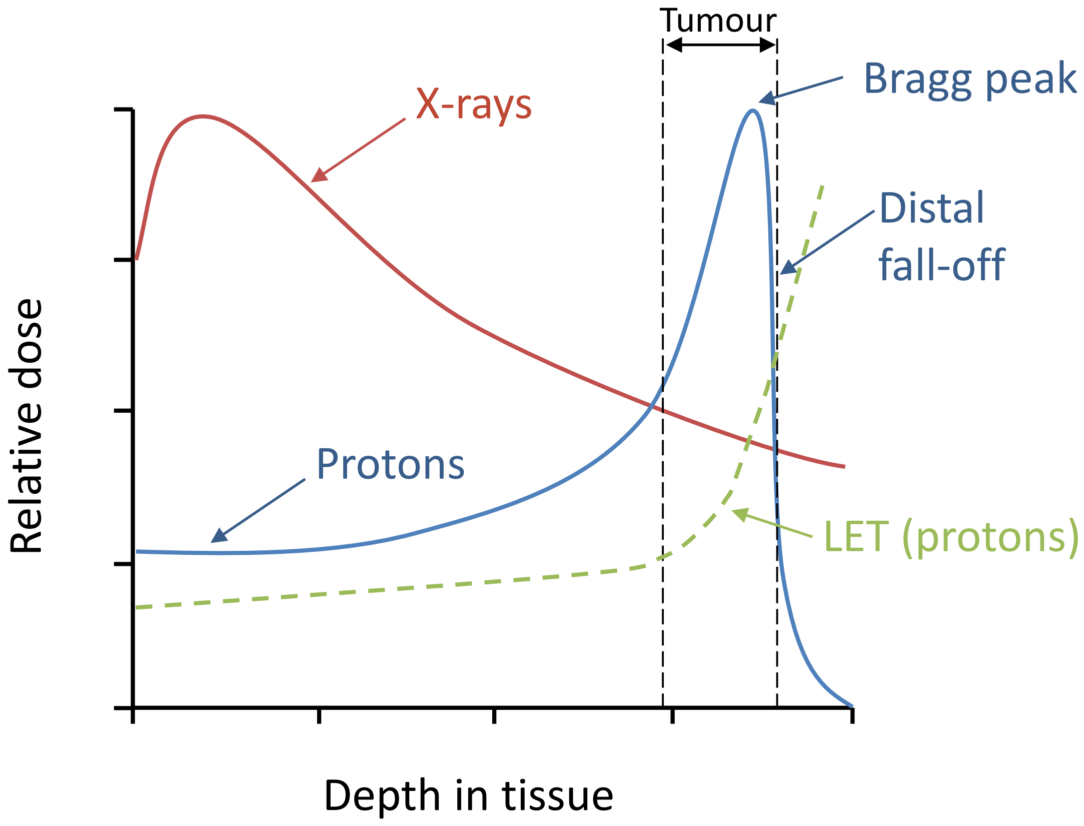
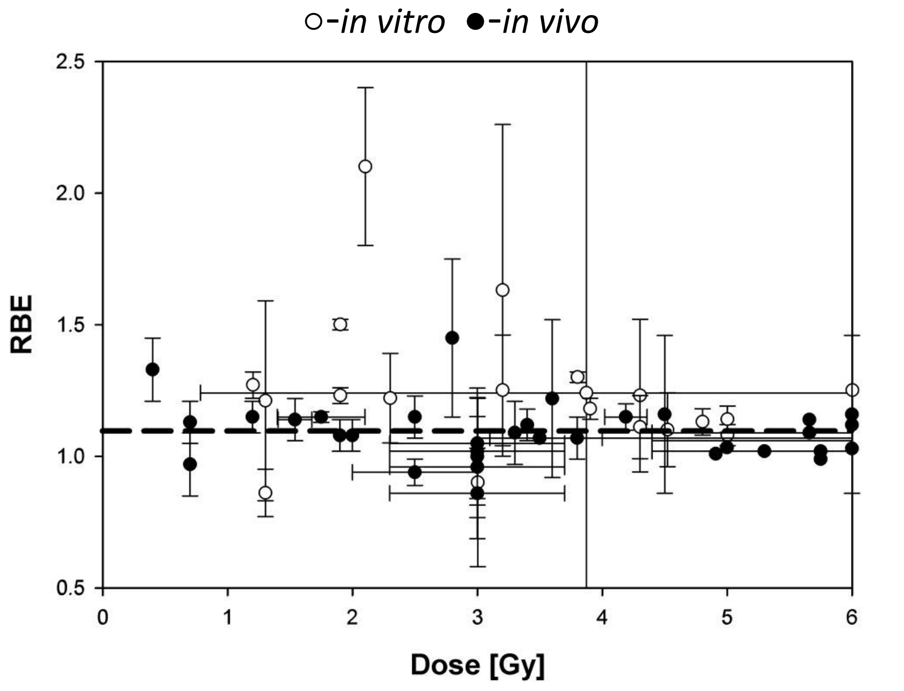
**University of Liverpool**

# 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***

# 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.

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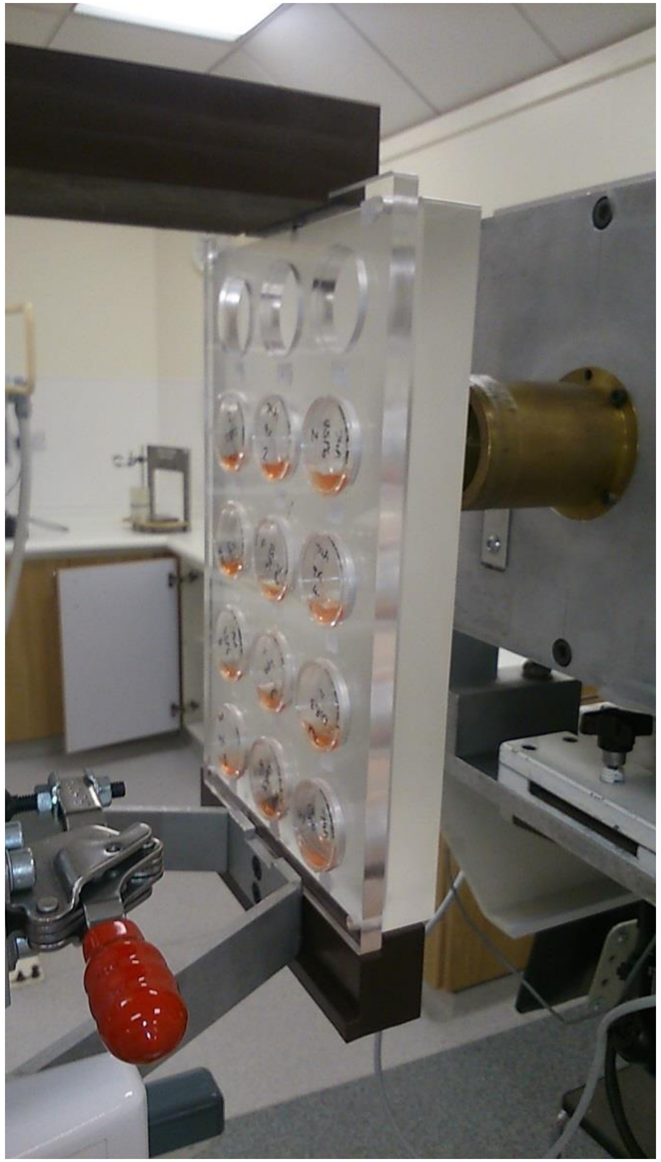
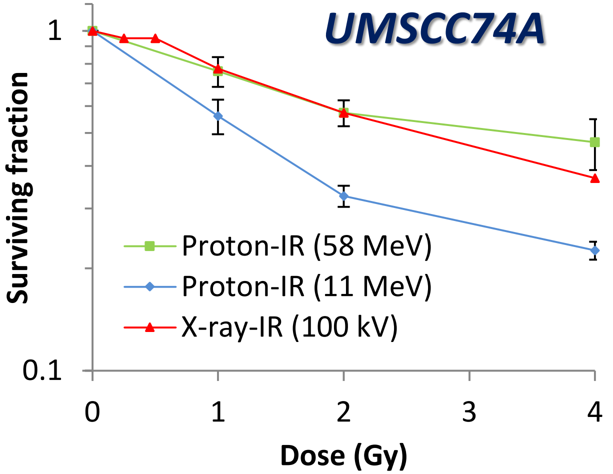
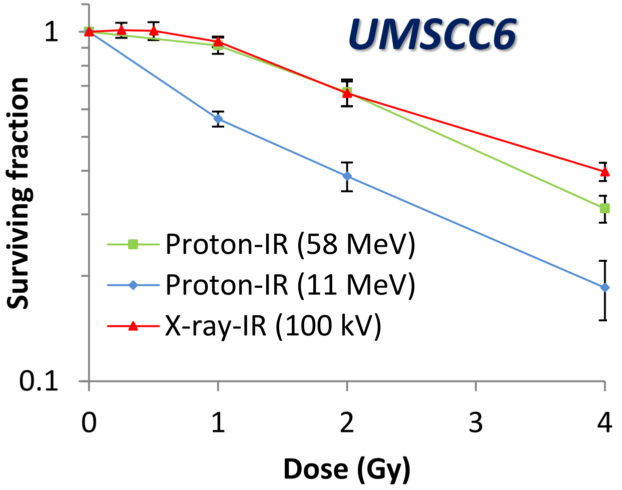
# Proton beam and radiobiology facilities at the Clatterbridge Cancer Centre (CCC)



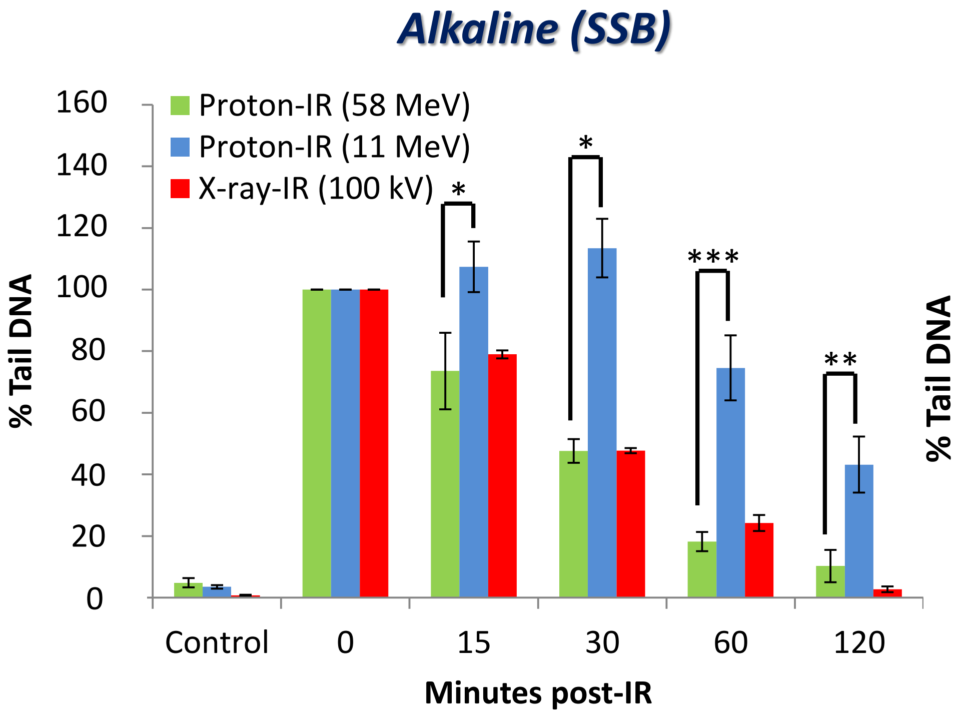
# "Relatively" high-LET protons cause a decrease in HNSCC cell survival due to CDD formation compared to low-LET protons



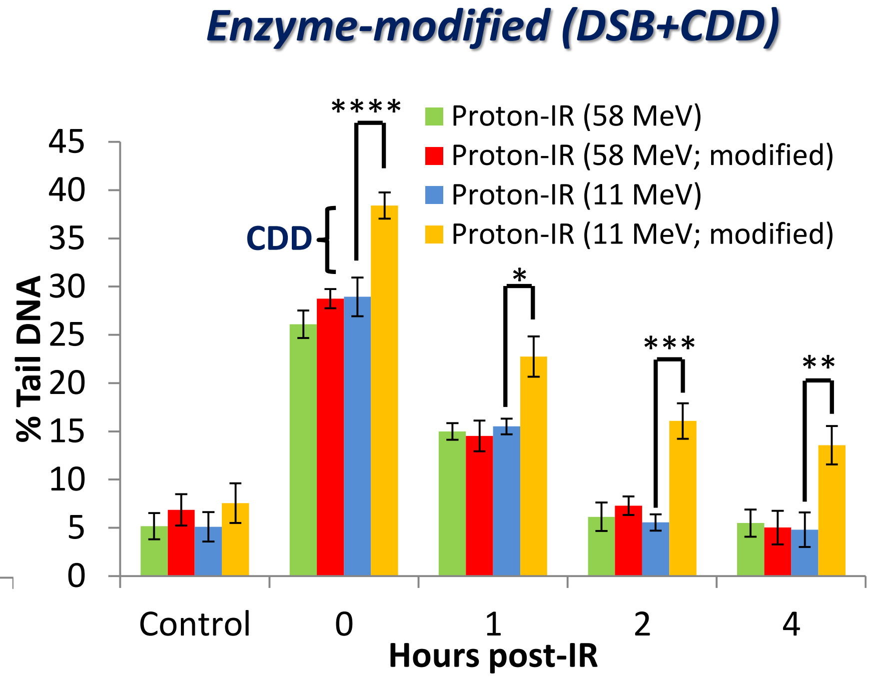

SF2, p<0.02; RBE=1.7




SF2, p<0.01; RBE=1.9




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

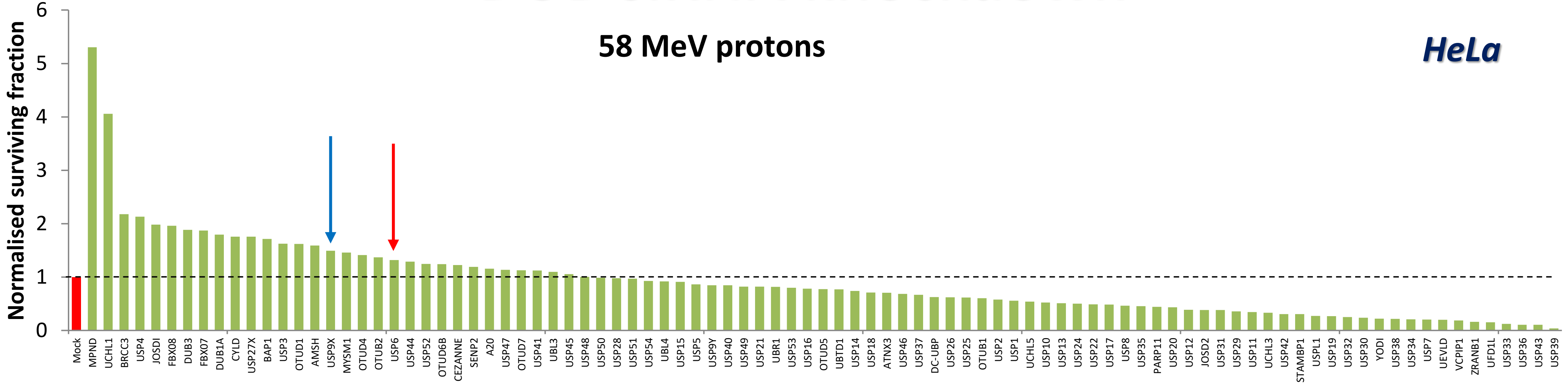


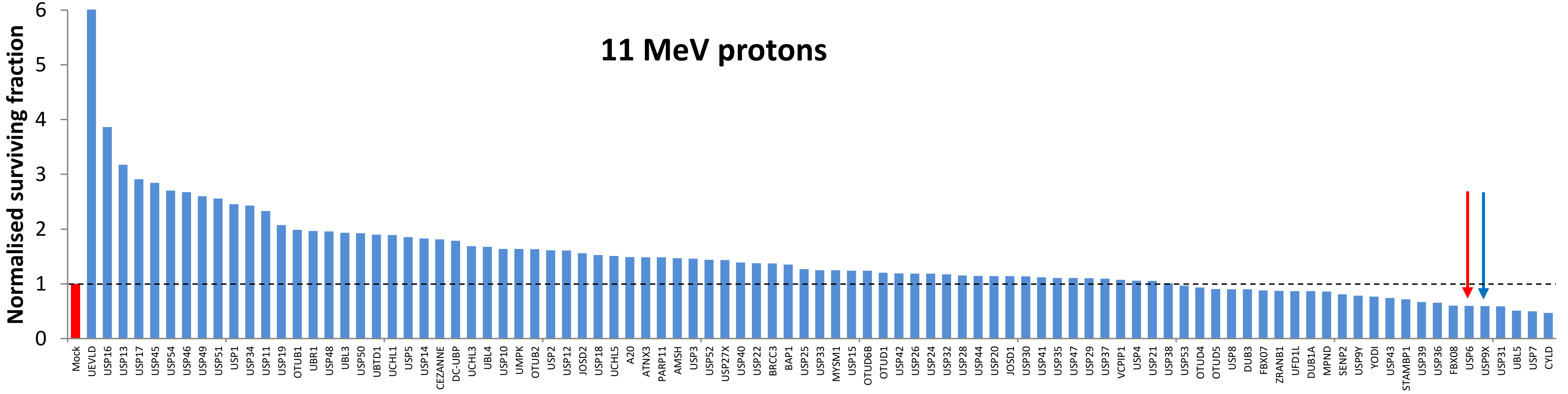

*p<0.02, **p<0.01, ***p<0.005, ****p<0.001

**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***

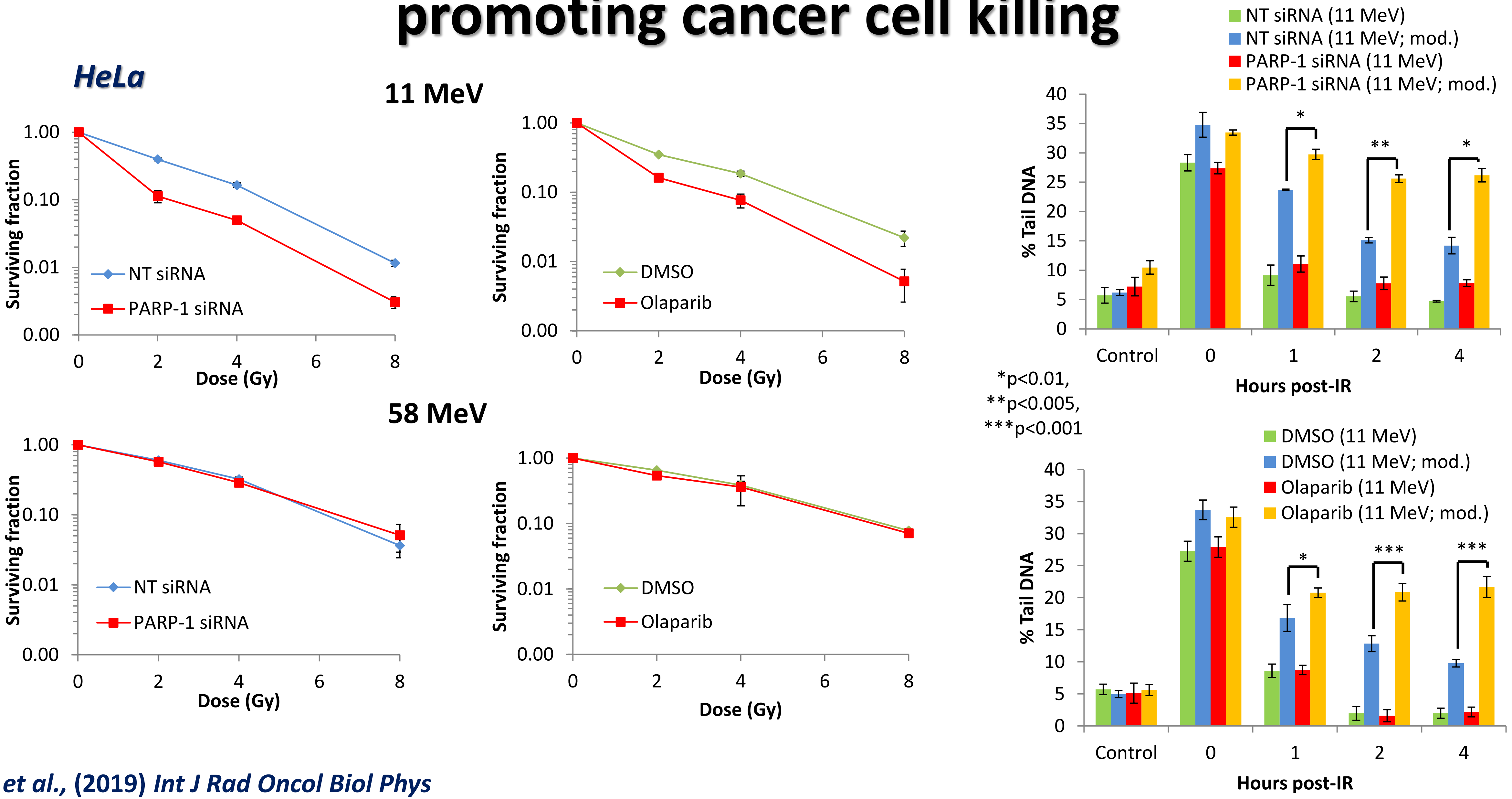
# Modulation of proton-induced cellular sensitivity following DUB siRNA knockdown



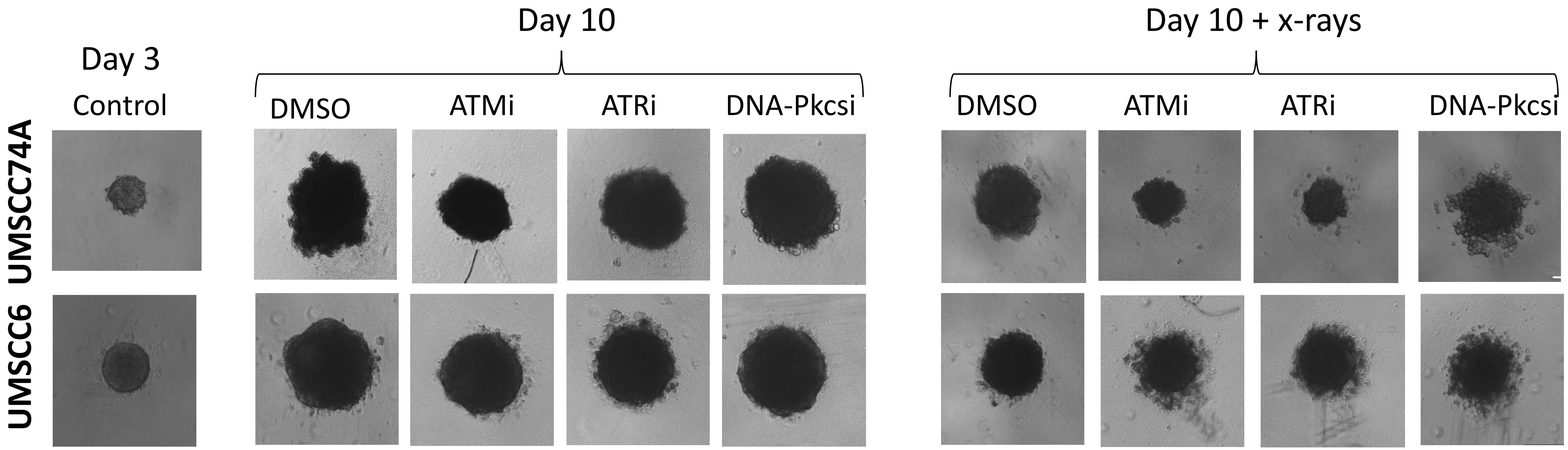

Carter *et al.*, (2019) *Int J Rad Oncol Biol Phys*
Nickson, Fabbrizi *et al.*, (2021) *Front Oncol*

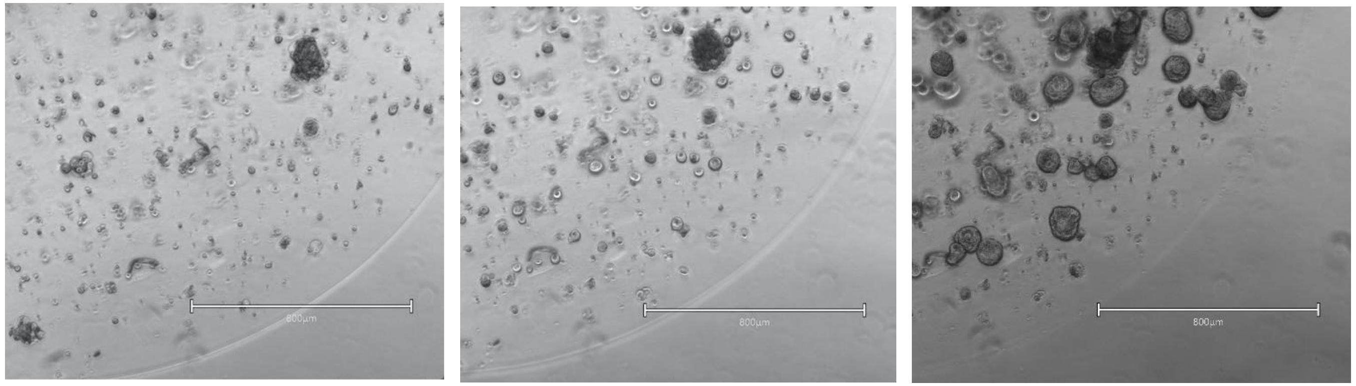
# Targeting PARP-1 synergies with relatively high-LET protons in promoting cancer cell killing




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

# Utilising 3D models of HNSCC with photons and protons



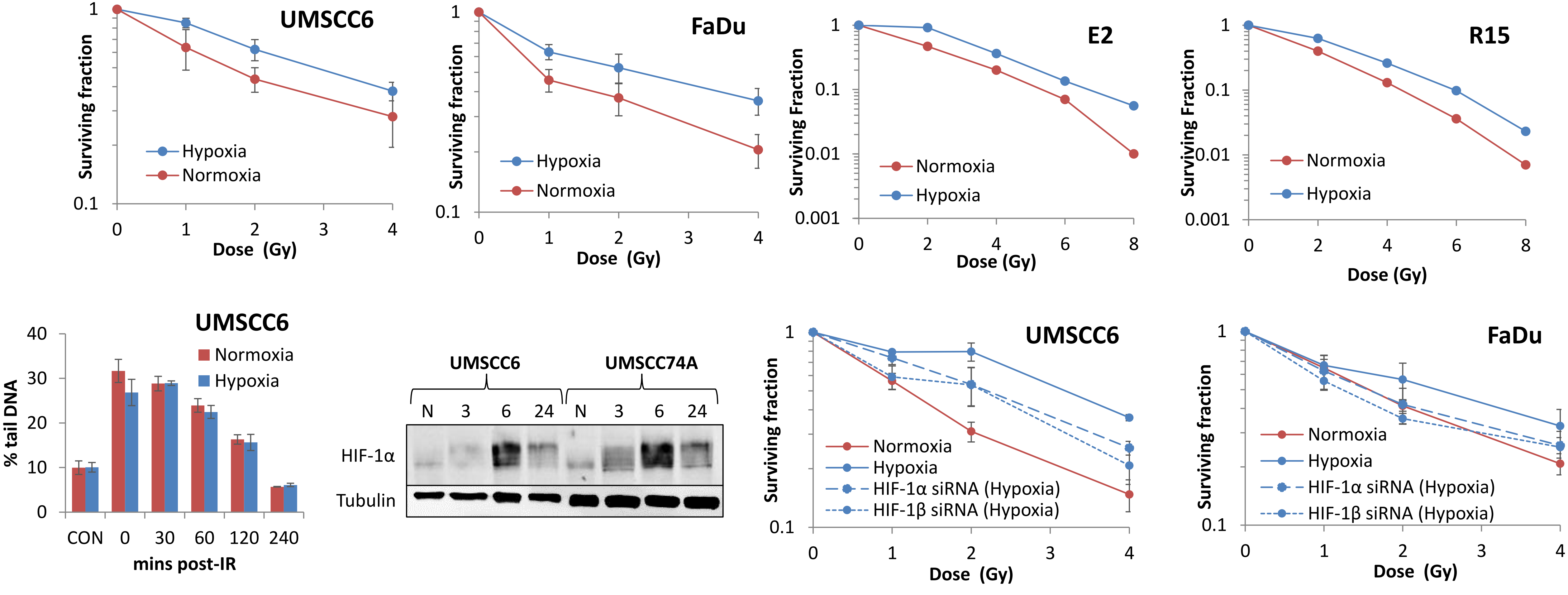
**Day 1** **Day 4** **Day 8**

**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.


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

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

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

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

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

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# 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).
- 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.

# Summary

## Biological questions to be addressed

- More substantial investigations into the radiobiology of particle ions in defined 2D/3D preclinical normal/tumour model systems.
- Uniquely positioned to investigate novel beam delivery (e.g. FLASH and minibeams) and to define the biology behind these phenomenona.
- Enable clinically-relevant dose fractionation experiments in preclinical models.
- Investigate combinatorial treatments (e.g. targeted DDR/IO drugs and inhibitors, stimulate high-throughput screening experiments).

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