Radiobiological motivation for LhARA

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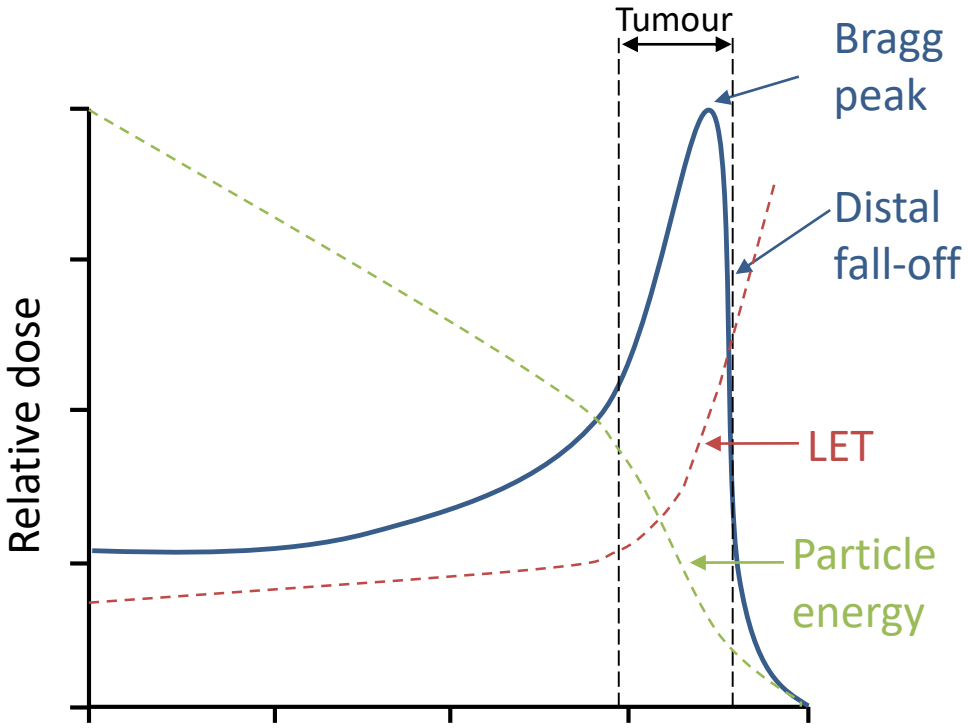
Radiotherapy in cancer treatment

- ~50 % of all cancer patients will receive radiotherapy.
- Conventional (photon) radiotherapy is the still the most effective treatment for solid tumours (e.g. head and neck).
- Dose rates of ~1-5 Gy/min utilised.
- Significant irradiation of normal tissues and organs at risk in proximity to the tumour being treated.
- Biological factors including oxygen (hypoxia) and inherent radioresistance of tumours (e.g. glioblastoma) are a barrier to effective treatment.

Particle beam therapy (PBT)

- In contrast to conventional (x-ray) radiation, PBT can deliver energy within a finite region (termed the Bragg peak) which can directly target cancer cells.
- This limits radiation dose to proximal normal, healthy tissues and organs at risk.



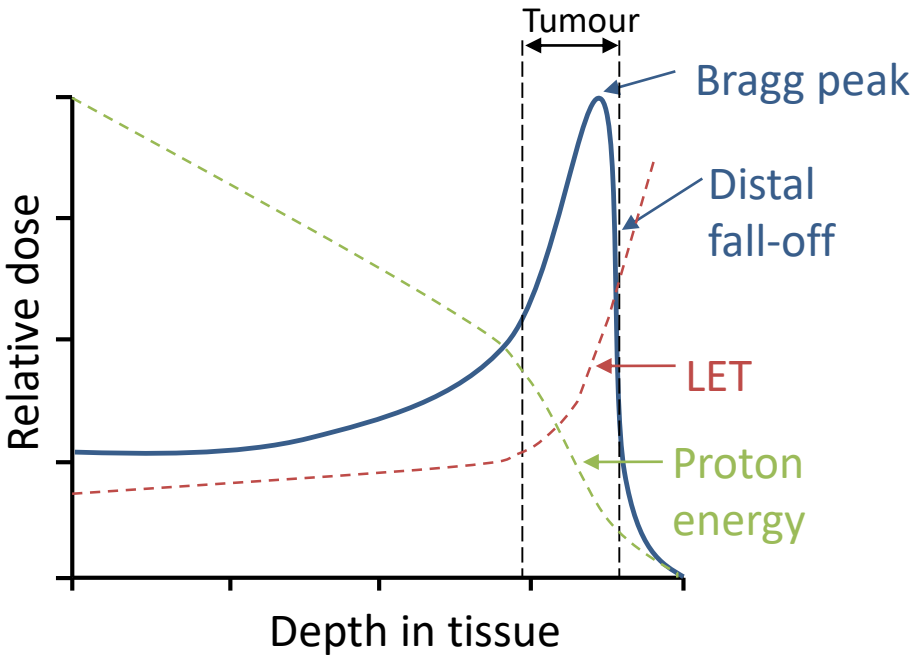
Vitti and Parsons (2019) Cancers

- Currently, ~90 PBT centres worldwide and 40 in construction demonstrating the importance of this precision radiotherapy.

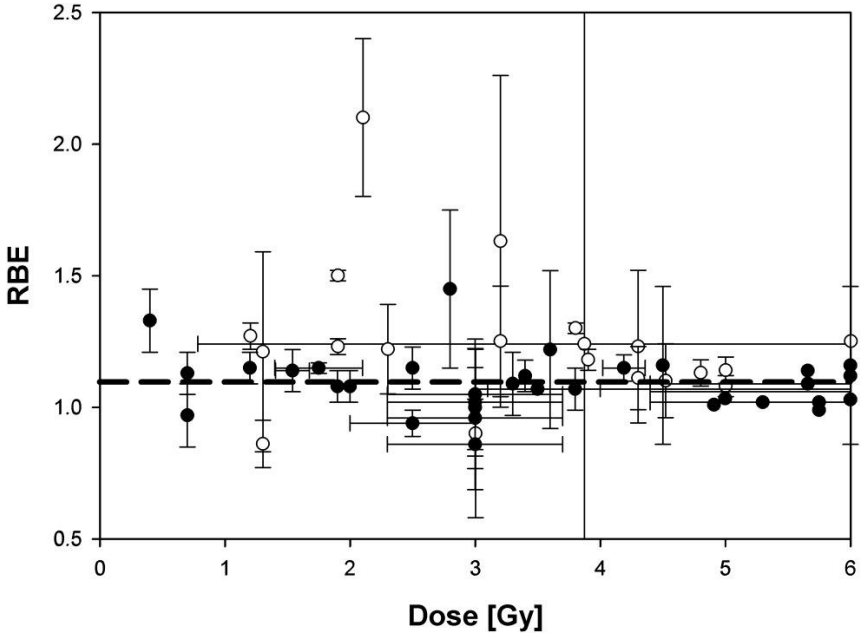
Eye Proton Therapy Centre and Radiobiology Research Facilities at Clatterbridge

- Successfully treating patients (currently ~300/year) with cancers of the eye for >25 years with 60 MeV proton beam.
- Limited time and proton beam access due to patient treatments.
- Limited *in vitro* capabilities and unable to perform *in vivo* research.

Biological uncertainties with particle radiotherapy



Vitti and Parsons (2019) Cancers



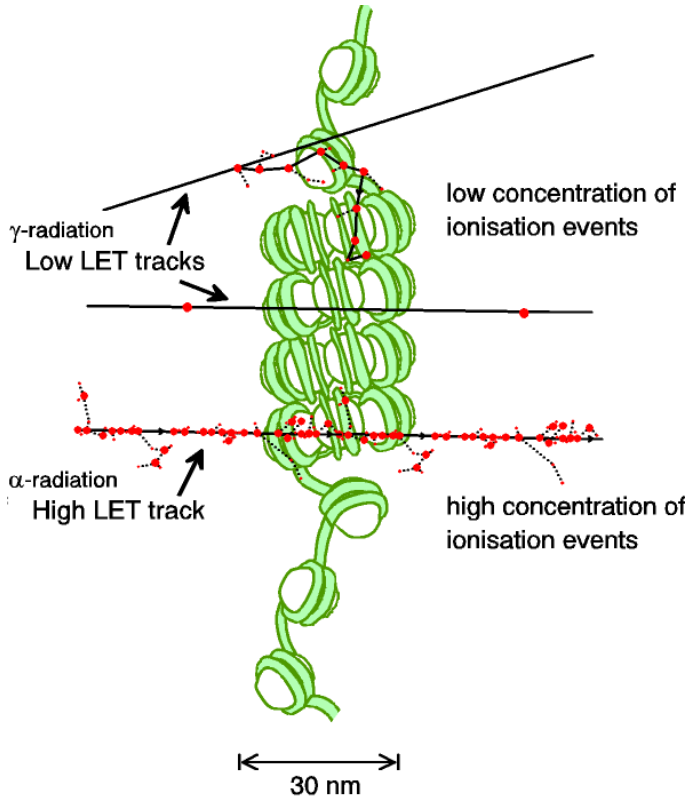
Taken from Paganetti and van Luijk (2013) Sem Rad Oncol

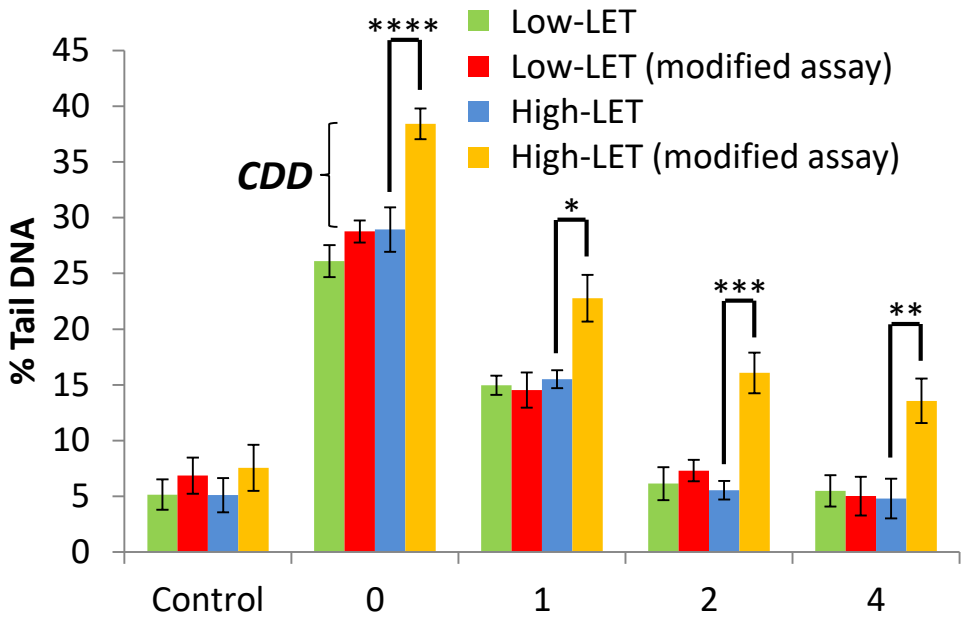
A constant relative biological effectiveness (RBE) value of 1.1 is used in clinical practice for protons. However, there is a large uncertainty with using this approach as RBE is variable and dependent on many factors, including:-

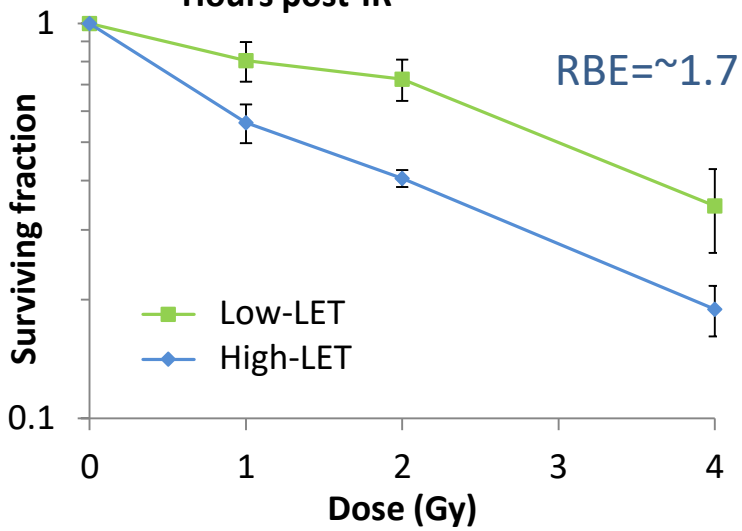
- Proton energy (therefore linear energy transfer, LET) and dose/dose rate.
- Radiosensitivity/radiobiology of the specific tumour tissue (e.g. based on DNA repair capacity, hypoxia and tumour microenvironment).
- Biological end-point examined (e.g. clonogenic survival, tumour growth delay).

Further research exploiting the biological impact of particle ions is vital for investigating RBE, and thus improving clinical use of PBT.

DNA damage and relationship to LET



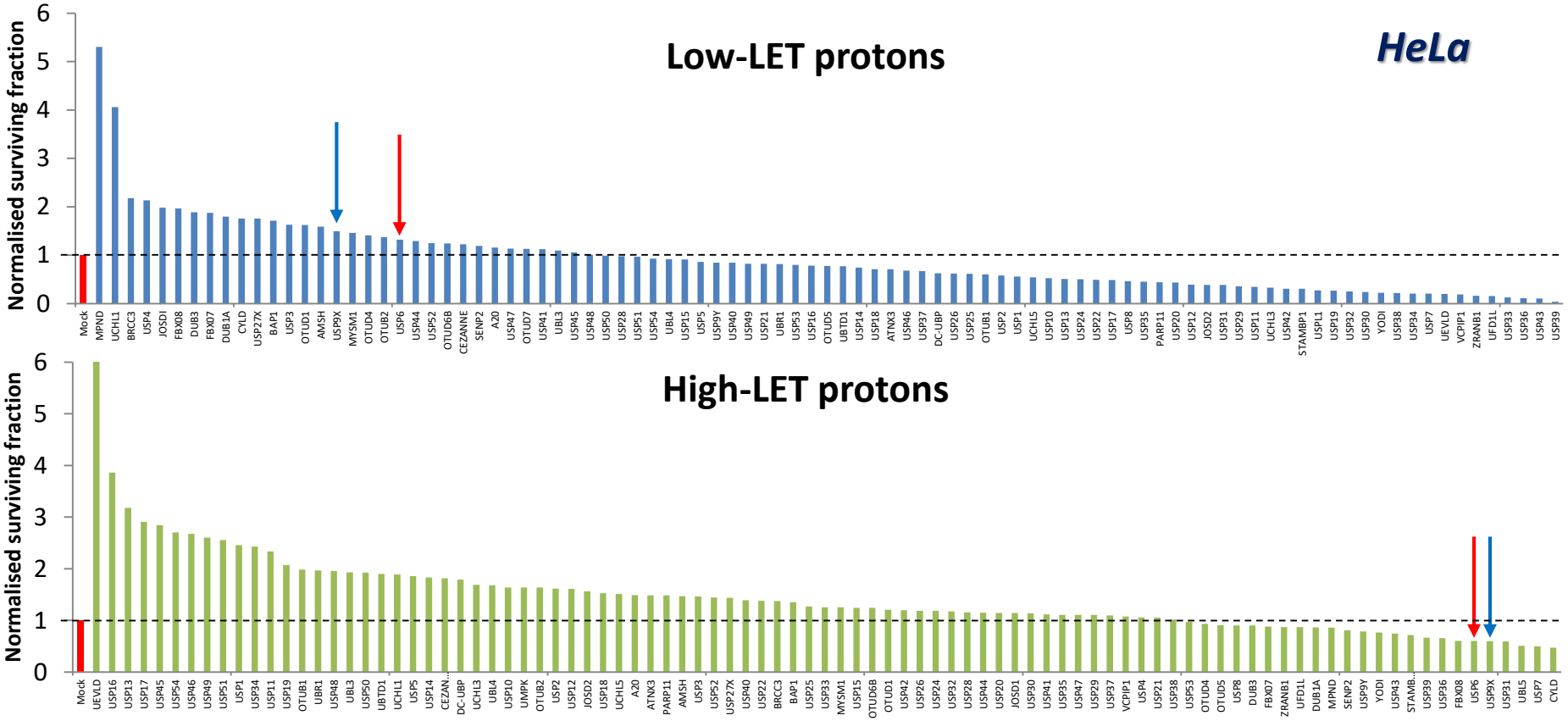




- Low-LET radiation produces repairable DNA damage (e.g. single and double strand breaks).
- High-LET radiation generates increased amounts of complex DNA damage (containing multiple DNA lesions) that are more difficult to repair, utilises multiple DNA repair pathways, and which can enhance cell death.

Carter et al, and Parsons (2018) IJROBP
Carter et al, and Parsons (2019) IJROBP

Modulation of proton-induced cellular sensitivity following siRNA knockdown screening



- Significant variability in the response of cells to low and high-LET protons dependent on cellular proteome.
- Will identify specific cellular targets (e.g. for combinatorial drugs/inhibitors) to exacerbate the effects of PBT.

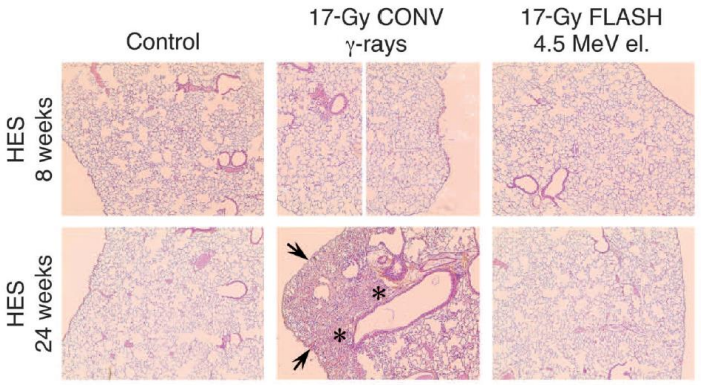
Carter et al, and Parsons (2019) IJROBP

FLASH radiotherapy

- **Using ultra high-dose rates (>100 Gy/s).**

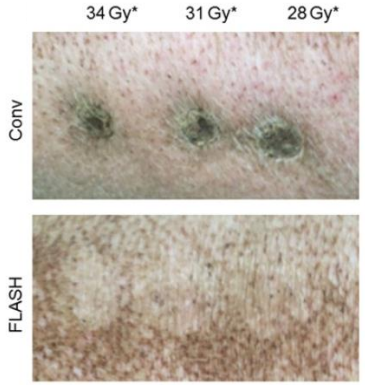
Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]



The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients

Marie-Catherine Vozenin[1], Pauline De Fornel[2], Kristoffer Petersson[1,3], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1,6], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2], and Jean Bourhis[1,6]



Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

- However, the mechanism of the FLASH effect is unclear (role of oxygen?).
- Impact of FLASH on specific tumour models not well defined.
- Effect of FLASH photon vs protons (and impact of LET), not been demonstrated.

Further research exploiting the biological impact of FLASH on appropriate *in vitro* and *in vivo* models is important for translation to the clinic.

Challenges and opportunities for PBT radiobiology research

Challenges

- The radiobiology of PBT at the molecular and cellular level is still not entirely understood (e.g. impact of LET, dose rate delivery).
- Other factors that impact on RBE of PBT not well defined (e.g. hypoxia, tumour microenvironment, drug-IR combinations, fractionated doses, FLASH).
- More research required using specific and validated cancer models, plus relevant normal tissue models, *in vitro* (e.g. 3D spheroids/organoids) and *in vivo*.
- Significant lack of access to PBT facilities for radiobiology research.
- Current facilities not fully equipped for *in vitro*, but more so *in vivo* experiments.

Opportunities with LhARA

- Highly accessible facility for both *in vitro* and *in vivo* particle ion radiobiology research, capable of analysing a multitude of biological end-points.
- Enhance our understanding of the radiobiological effects of particle ions (protons and carbon ions), including examining dose delivery (FLASH) and combinatorial treatments through high-throughput screening.
- Significant opportunity to develop research that will have a major Worldwide impact through the optimisation and personalisation of cancer treatments using PBT in the clinic.

Feedback from Yolanda Prezado

- **LhARA is a very promising facility which would offer unique beam features and infrastructure for radiobiology research.**

The main characteristics to be highlighted are:-

Flexibility

Flexible temporal and spatial beam structure allowing exhaustive investigations of beam parameters (pulse length, repetition rate, instantaneous dose, FLASH) on biological response utilising a stable beam.

Different beam species

One of the few places in the World to offer the evaluation of different particle ions (protons to heavier ions) within the same facility.

Accessibility

Greater accessibility of LhARA in comparison to clinical facilities, with greater flexibility (e.g. *in vitro* and *in vivo* experiments; dose fractionation; more complex biological end-points; immunotherapy/chemotherapy combinations).

- **LhARA has the potential to drive a change in current clinical practice by increasing the wealth of radiobiological knowledge.**