QUEEN'S UNIVERSITY BELFAST

THE PATRICK G JOHNSTON CENTRE FOR CANCER RESEARCH

Biology of Heavy Ions

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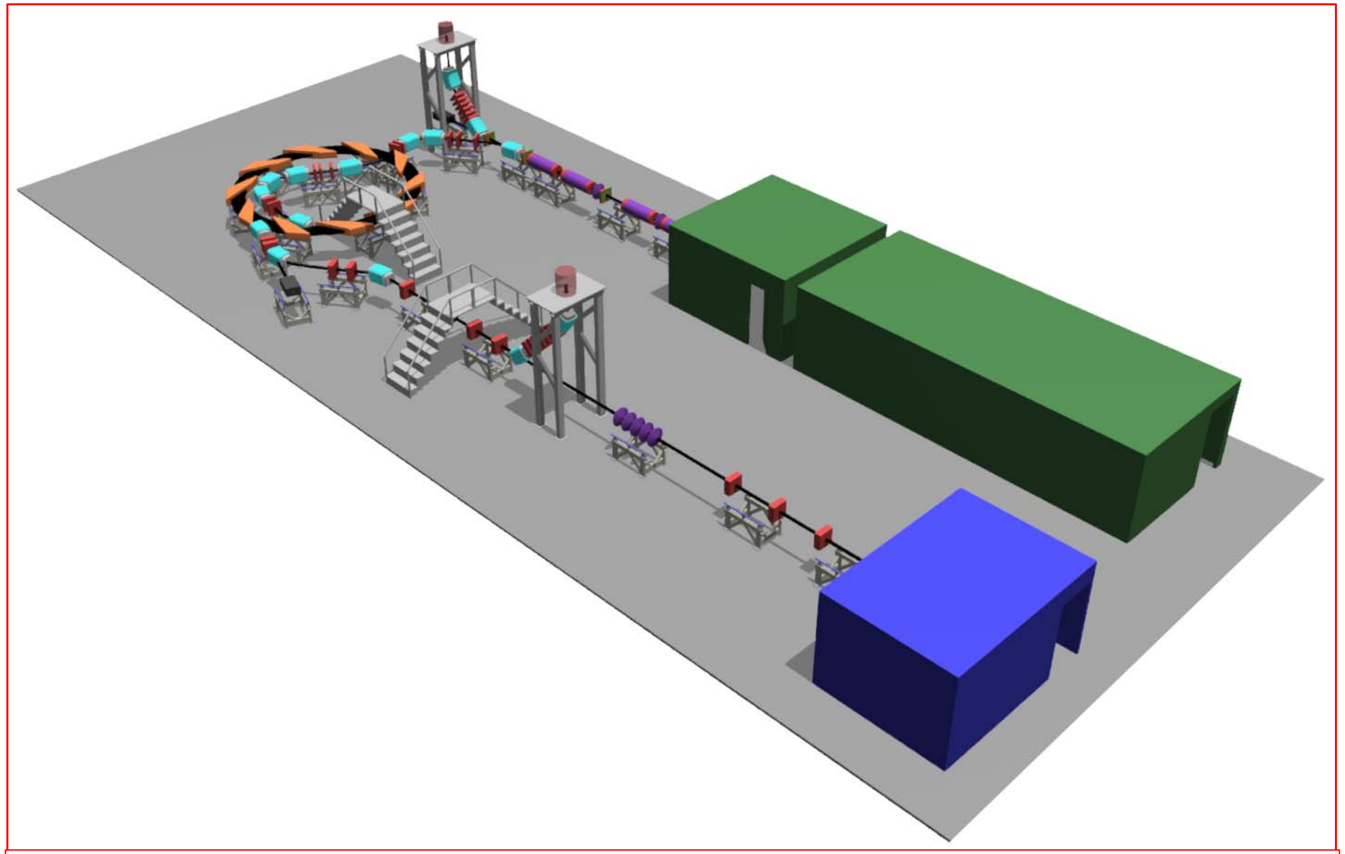
LhARA external review
26th October, 2022

Outline

- Heavy ion radiobiology
- Proof of concept studies with lasers produced ion beams
- Future potential

LhARA – Biology Capabilities

- Flexible source for *in vitro* and *in vivo* radiobiology
- Range of energies and ion species possible
- Flexibility in pulse delivery over space and time
- Cost effective alternative to synchrotron based facilities

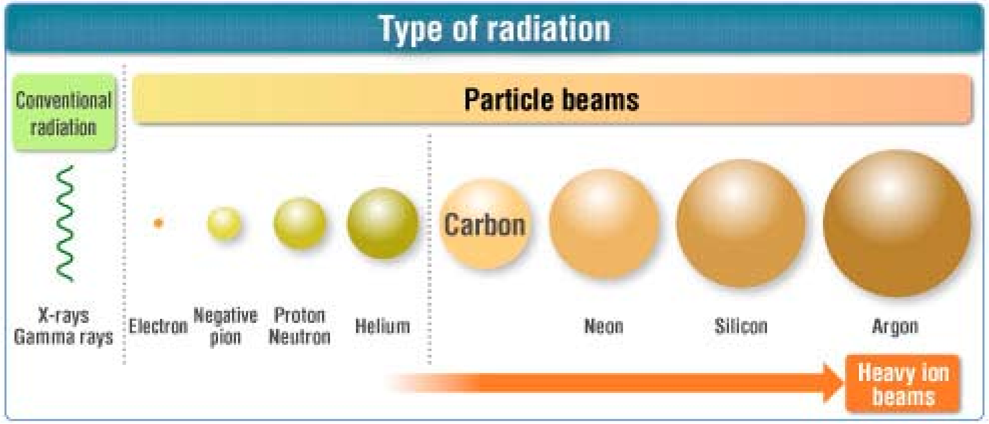


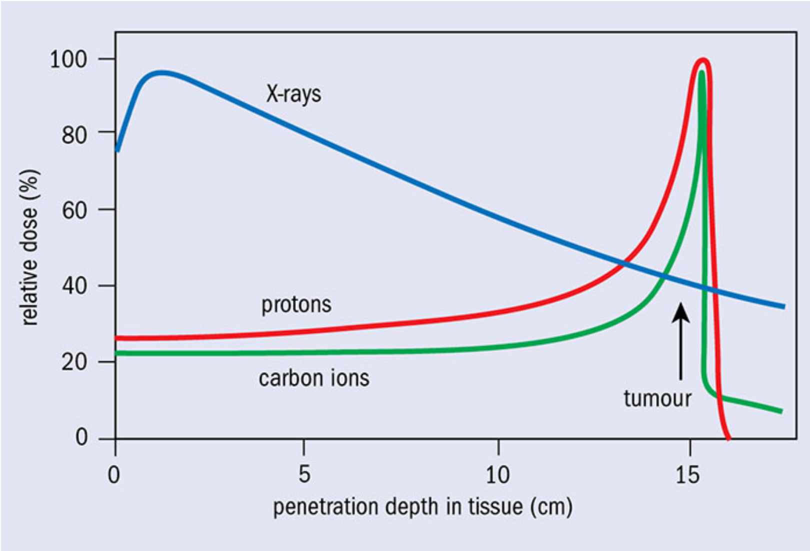
LhARA performance summary arXiv:2006.00493

	12 MeV Protons	15 MeV Protons	127 MeV Protons	33.4 MeV/u Carbon
Dose per pulse	7.1 Gy	12.8 Gy	15.6 Gy	73.0 Gy
Instantaneous dose rate	1.0×10^9 Gy/s	1.8×10^9 Gy/s	3.8×10^8 Gy/s	9.7×10^8 Gy/s
Average dose rate	71 Gy/s	128 Gy/s	156 Gy/s	730 Gy/s

Heavy ions

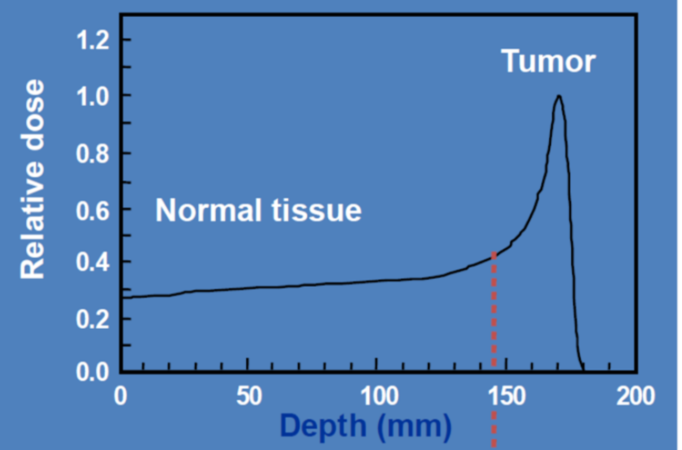
- A range of ions can be used for cancer therapy
- Alongside protons, carbon ions are commonly used
- Advantages include lower entrance dose and increased LET (and Relative Biological Effectiveness)

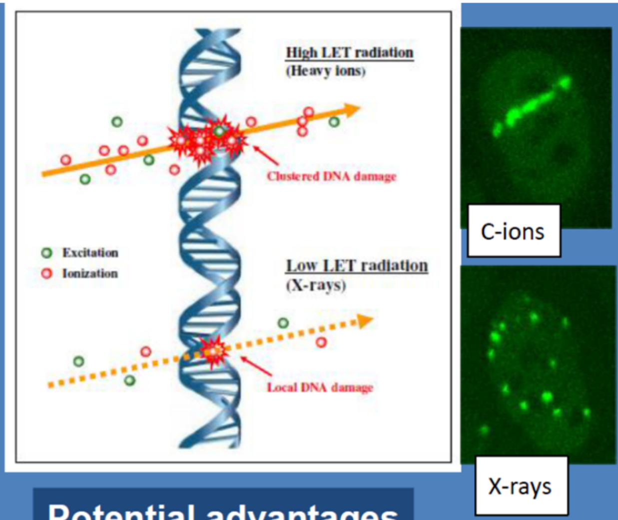




Heavy ion radiobiological advantages

- A range of factors give ions radiobiological advantages
- LhARA will allow systematic testing of these in advanced biology models





	Normal tissue	Tumor	Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumors
Cell-cycle dependence	high	low	Radioresistant (S) phase cells are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumour
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Immune effects	Weak	Strong	Systemic effects in combination with immunotherapy

Tinganelli and Durante, 2022, *Cancers* **12,** 3022.

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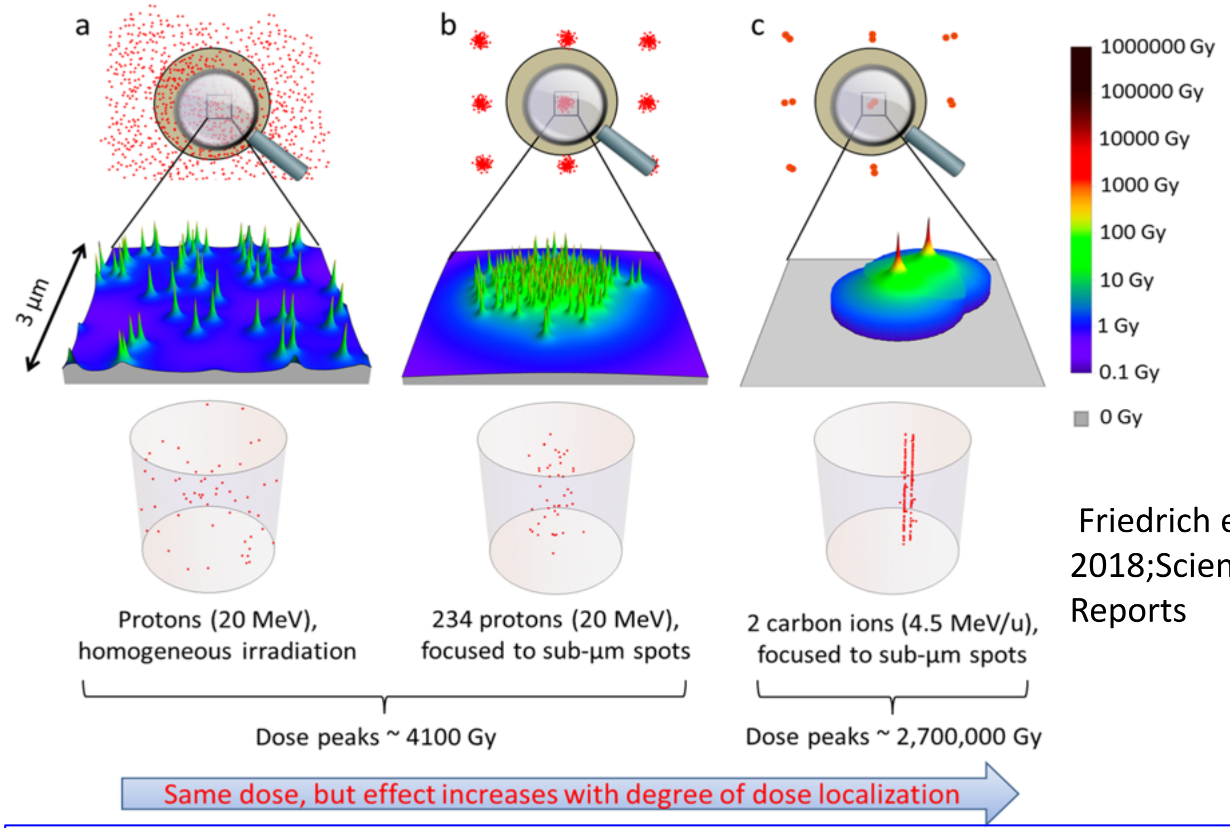
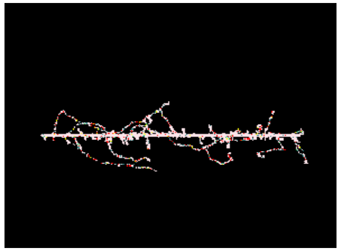
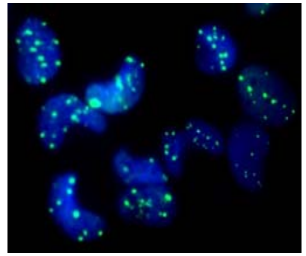
Spatial patterns – sub micron



Friedrich et al , 2018;Scientific Reports



10 MeV Carbon ions track lateral view



10 MeV/n Carbon ion induced DNA Damage in GBM stem Cells

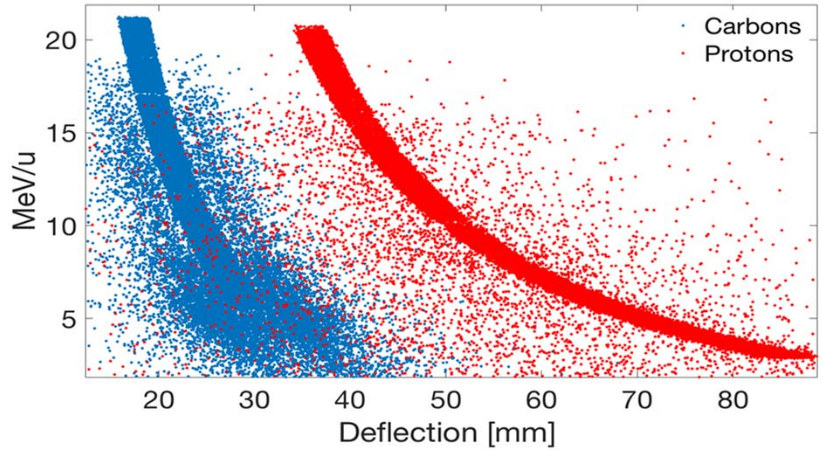
Due to the highly localized dose effects of carbon ions they are effective for radiotherapy , e.g. only 2 carbon ions deposit 700 times more dose than homogeneous or 234 protons at sub-µm scale

- LhARA will be a key tool to probe subcellular dose distributions of ions

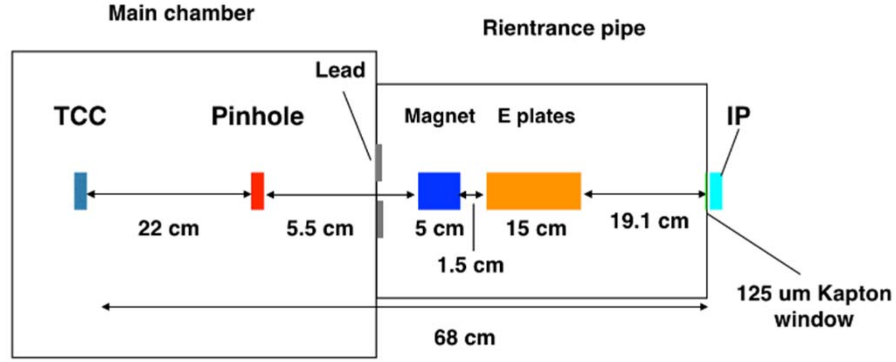
Can lasers produce heavy ion beams for radiobiology?

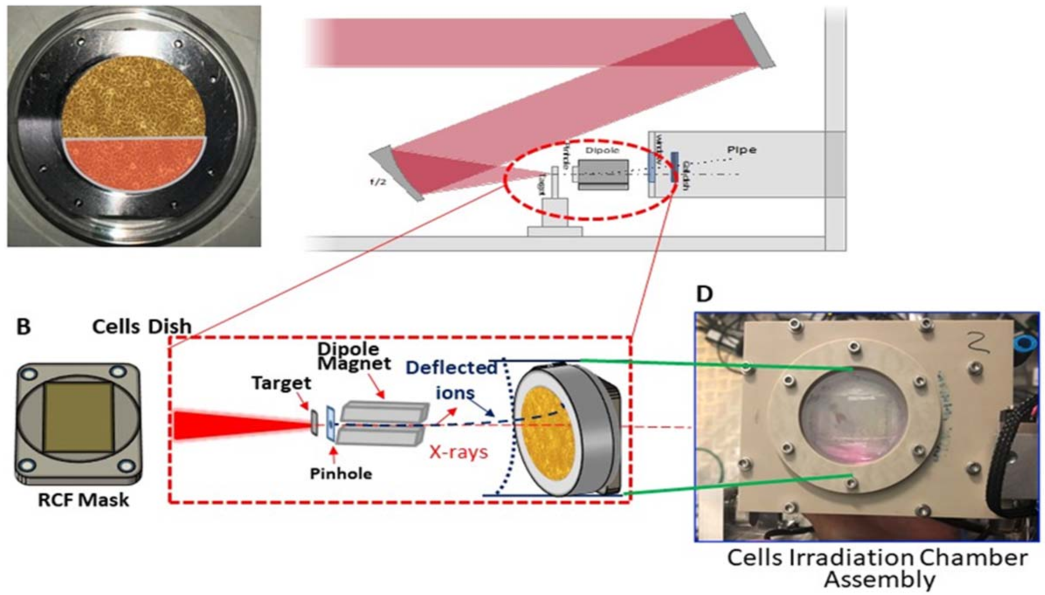
Proof of concept - Laser produced carbon ions - setup

- Using TNSA, carbon ions of up to 30 MeV/n have been accelerated using the STFC Gemini laser



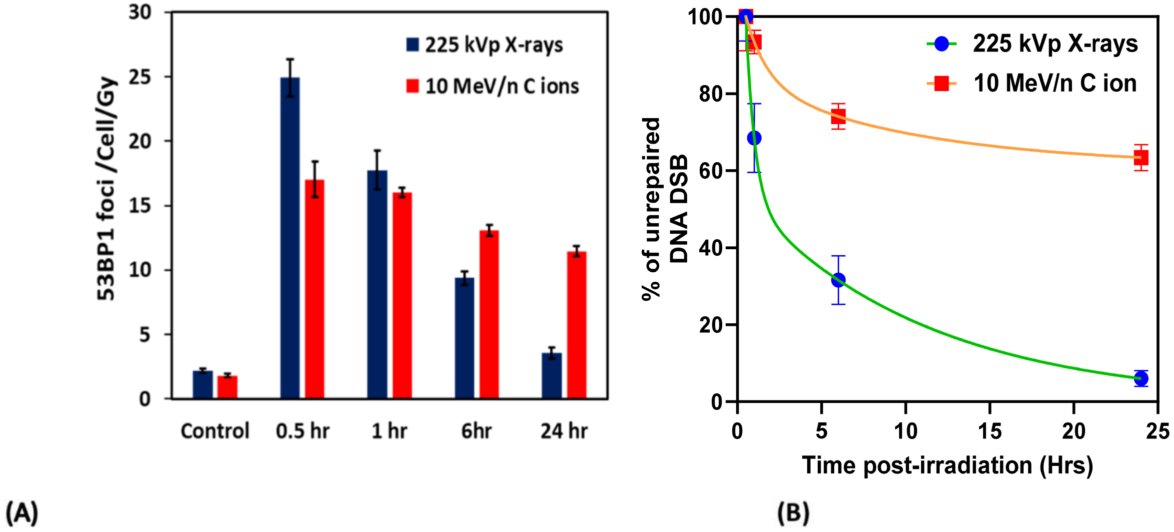
McIlvenny *et al.*, 2021 *Phys Rev Lett*, **127,** 194801.
Milluzzo *et al.*, 2020 *J Phys Conf Ser* **1596,** 012038.
Chaudhary *et al.*, submitted.

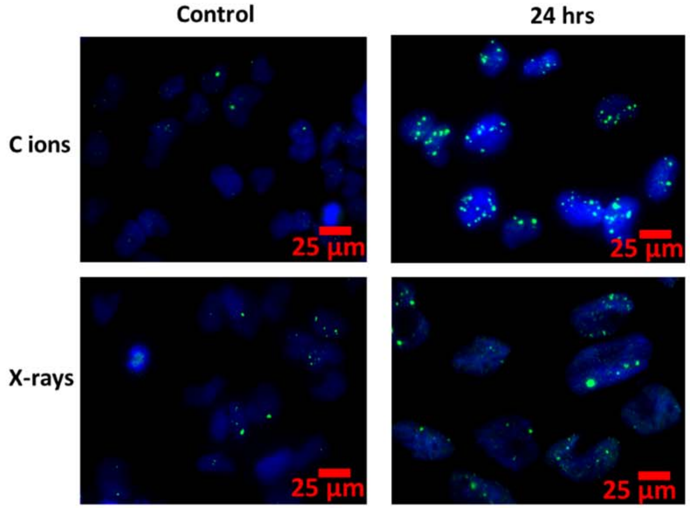


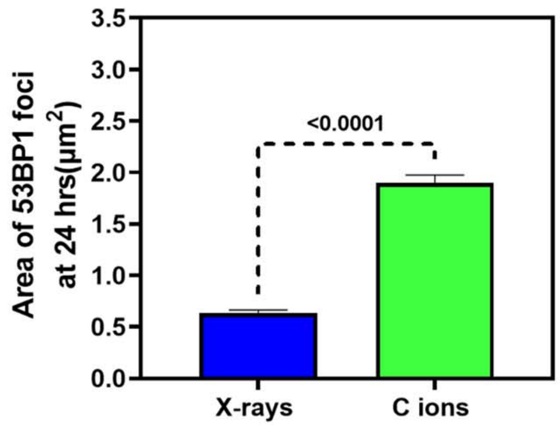


Proof of concept - Laser produced carbon ions – cell irradiations

- Single pulse 1 Gy exposures
- 2.5 x 10^9 Gy/s
- 10 MeV/n carbon ions (160 keV/µm)
- Radioresistant GBM stem cells
- Significantly reduced DSB repair
- Increased 53BP1 foci size







Chaudhary *et al.*, submitted

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A-SAIL ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS

Is their novel radiobiology at ultra-high dose-rate?

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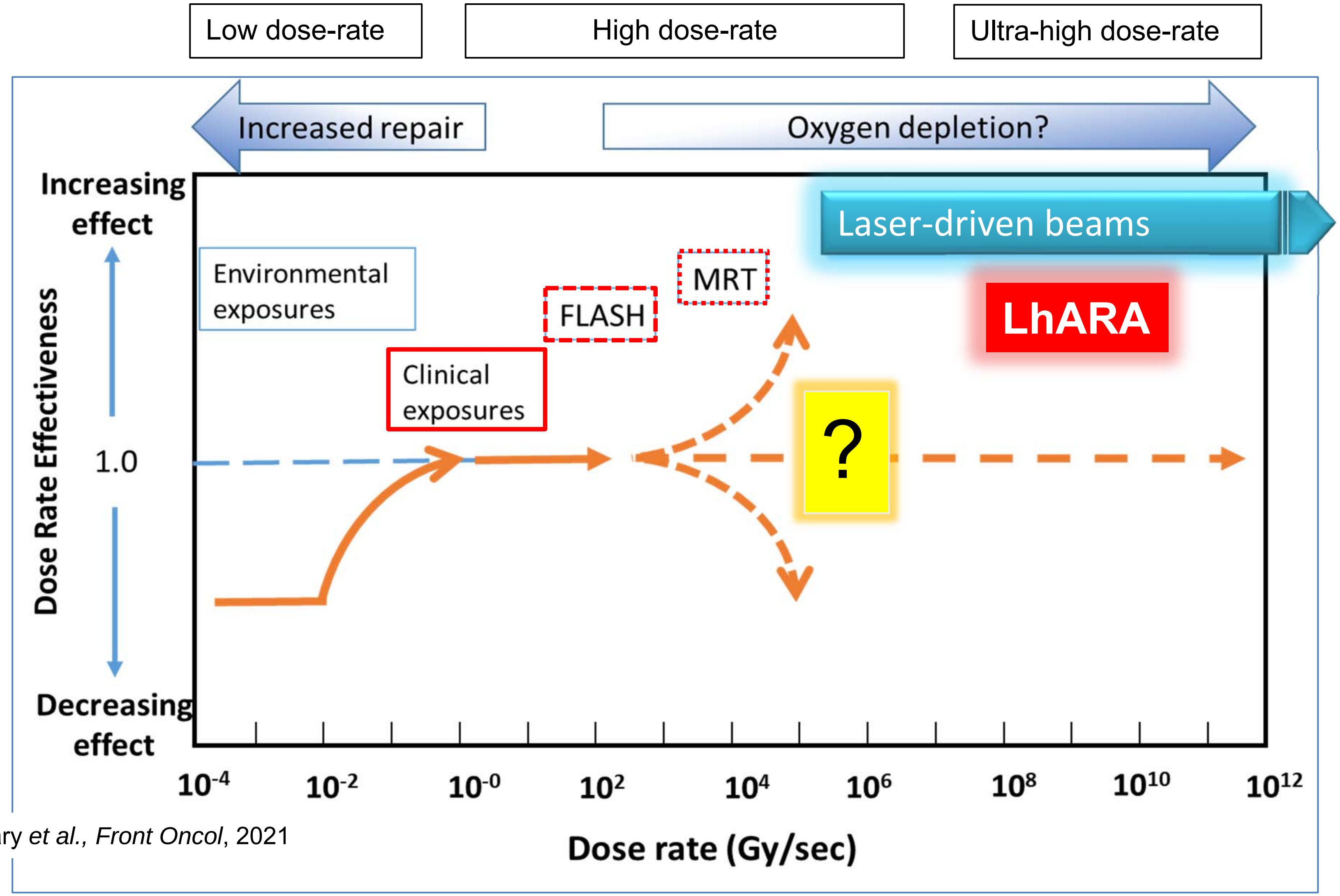
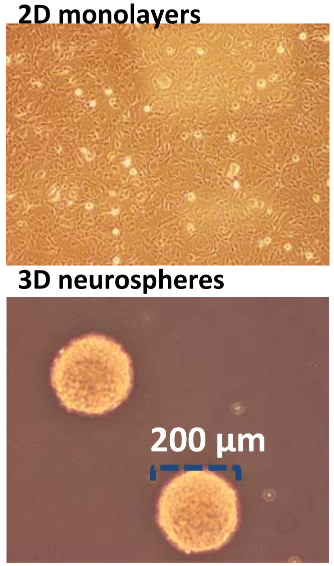
Dose-rate effects

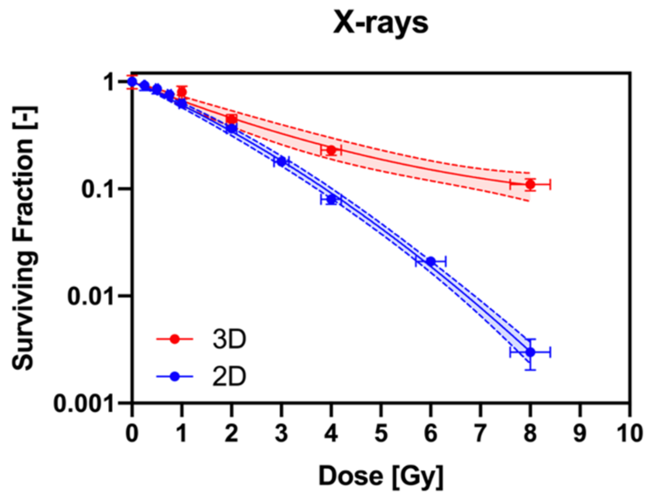


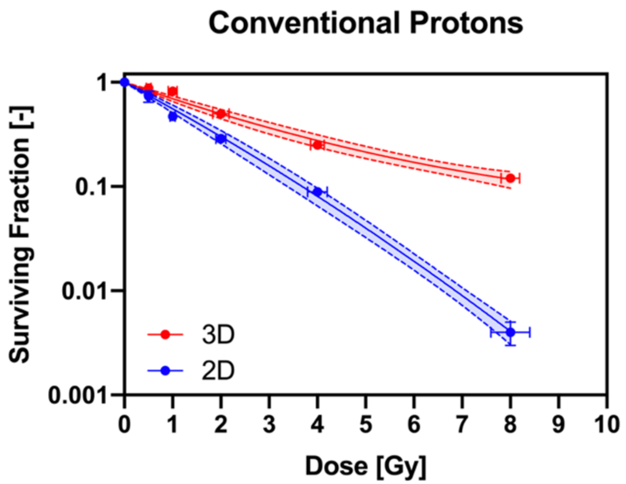
Chaudhary *et al.*, *Front Oncol*, 2021

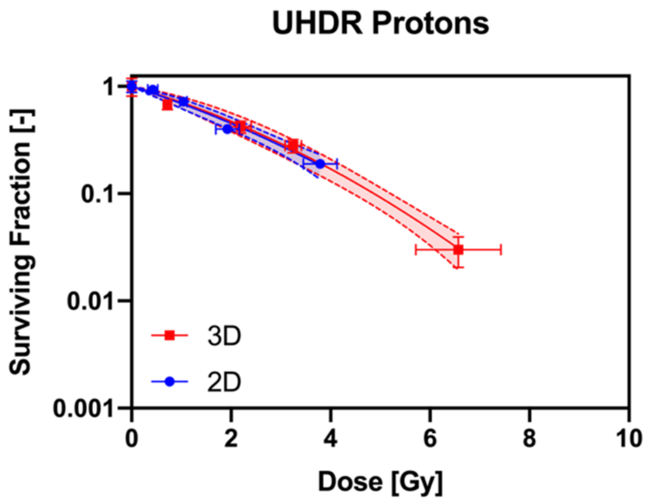
Proof of concept of ultra-high dose-rate effects

- 3D GBM neurospheres more radioresistant than 2D to X-rays
- Similar response to conventional protons (30 MeV, 4 Gy/min)
- 35 MeV laser accelerated protons at 1 x 10^{10} Gy/s
- UHDR reduced the radioresistance of 3D neurospheres
- Dose-dependent changes, likely that oxygen depletion plays a role





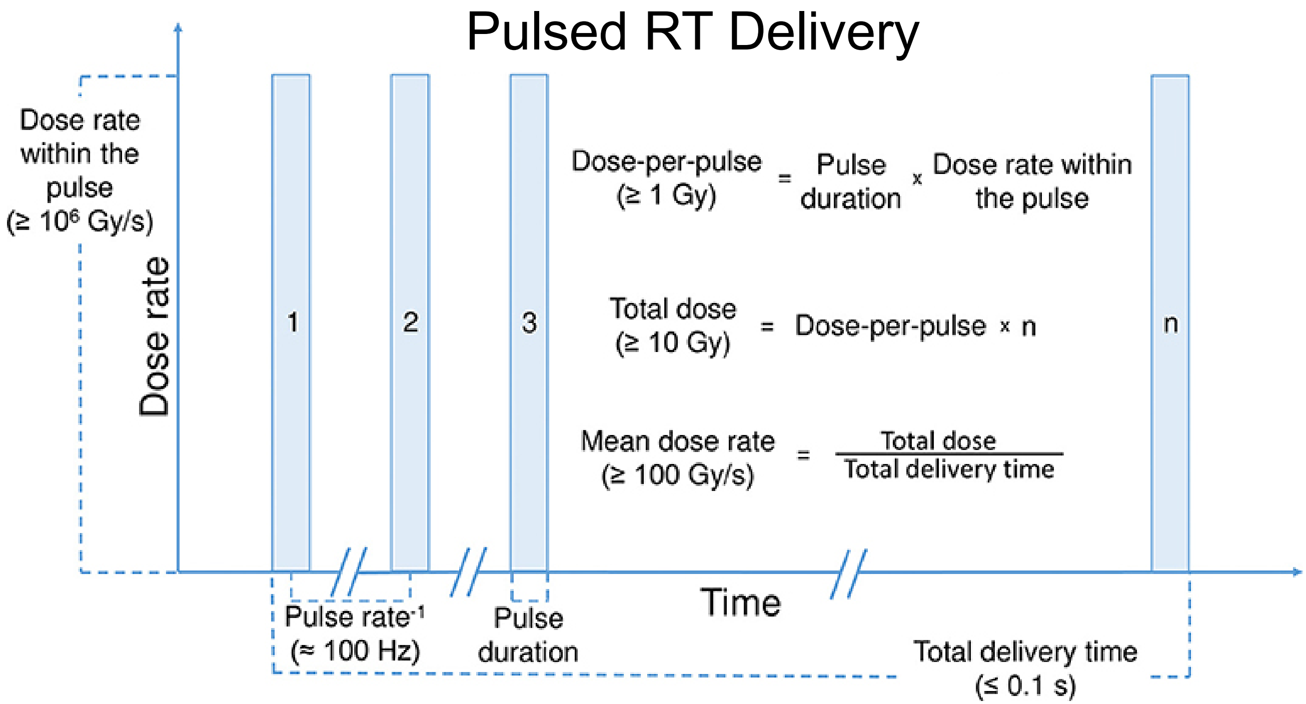




Odlozilik, Chaudhary, McMurray, Borghesi and Prise: *in preparation*

Dose-rate - Key Physical Parameters

- LhARA will allow systematic testing of dose-delivery patterns
- Total Dose
- Dose per pulse
- Frequency of pulses
- Overall exposure time
- Radiation type



From Wilson *et al.*, 2017 *Front Oncol*, **9,** 1563.

Temporal delivery of single shot laser driven ions can change the biological response of cells

LOA Group, Bayart *et al*, Scientific Reports, 2019
Dose rate: 1.5 x 10 ^{8} Gy/sec protons
Energy range: 1-6 MeV
Dose delivery mode: **multiple pulses**
Time interval between pulses : 3-60 seconds

SCIENTIFIC REPORTS

OPEN

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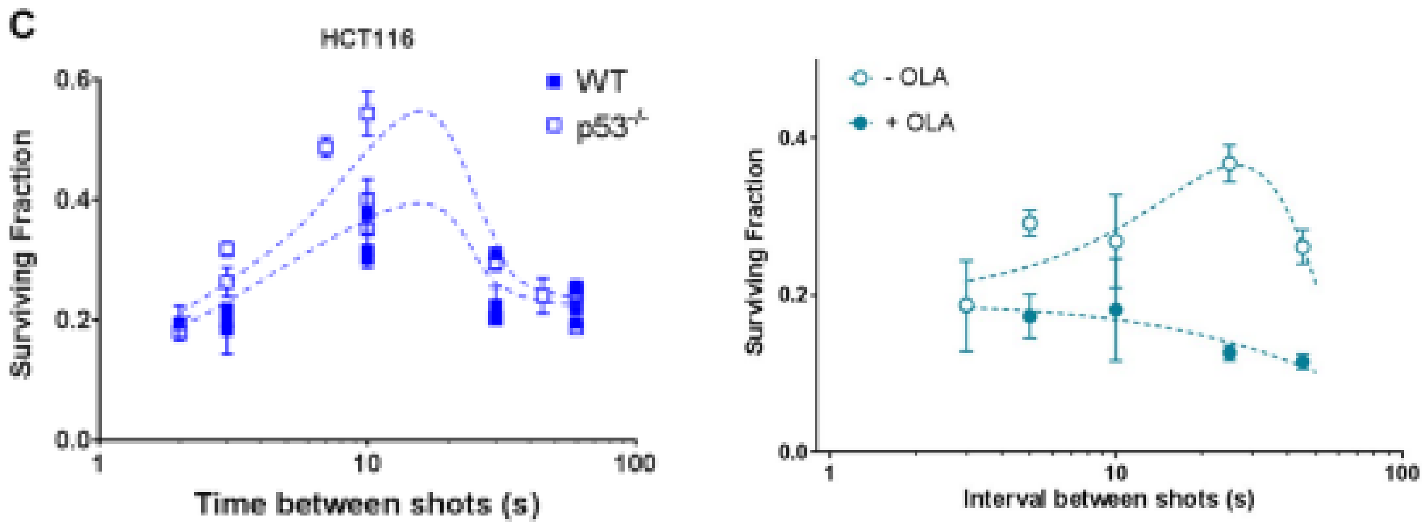
Fast dose fractionation using ultra-short laser accelerated proton pulses can increase cancer cell mortality, which relies on functional PARP1 protein

E. Bayart[1], A. Flacco[1], O. Delmas[1], L. Pommarel[1,2], D. Levy[1,3], M. Cavallone[1], F. Megnin-Chanet[4,5], E. Deutsch[4] & V. Malka[1,3]



Cell survival of cancer cell lines was found dependent on the bunch repetition rate of laser driven protons – **Biology plays a role**

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Novel biology with heavy ions and high dose-rate

- Studies now reporting carbon ion exposures at ~100 Gy/s, 240 MeV/n carbon, 15 keV/μm
- Improved normal tissue sparing
- Increased tumour control
- Increased control of distal metastasis
- LhARA will be able to do similar studies at much higher dose-rates

Radiotherapy and Oncology 175 (2022) 185–190

Contents lists available at ScienceDirect

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journal homepage: www.thegreenjournal.com

Original Article

FLASH with carbon ions: Tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

Walter Tinganelli [a], Uli Weber [a], Anggraeini Puspitasari [a], Palma Simoniello [b], Amir Abdollahi [c], Julius Oppermann [a], Christoph Schuy [a], Felix Horst [a], Alexander Helm [a], Claudia Fournier [a], Marco Durante [a,d,*]

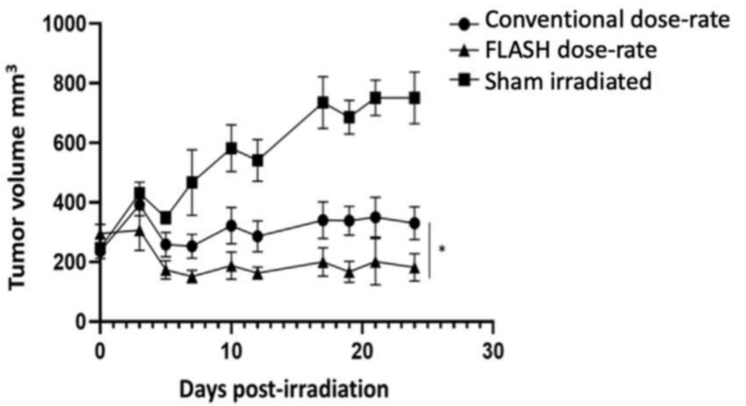


Fig. 2. Tumor growth of the osteosarcoma after irradiation with heavy ions. Ultra-high dose rate ^{12}C-ion irradiation produces a statistically significantly reduction in tumor volume compared to conventional dose rate.

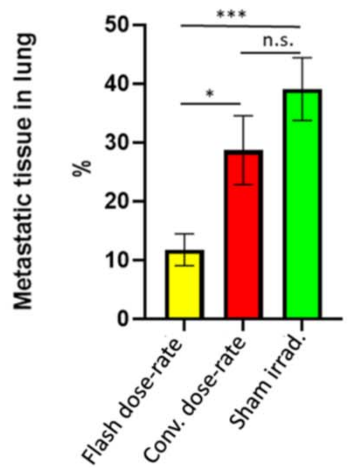
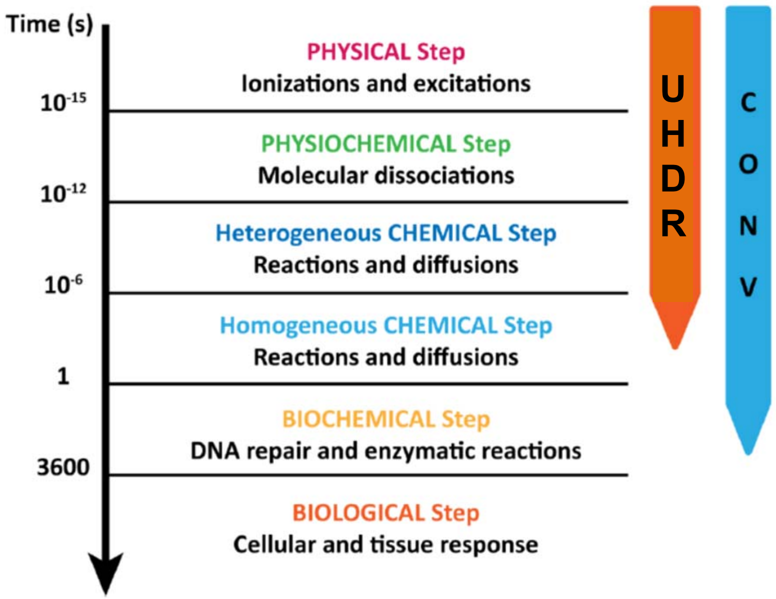
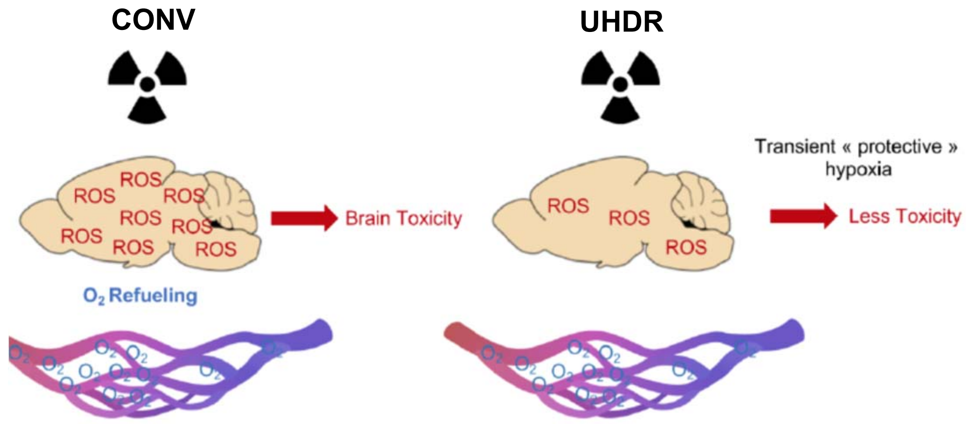
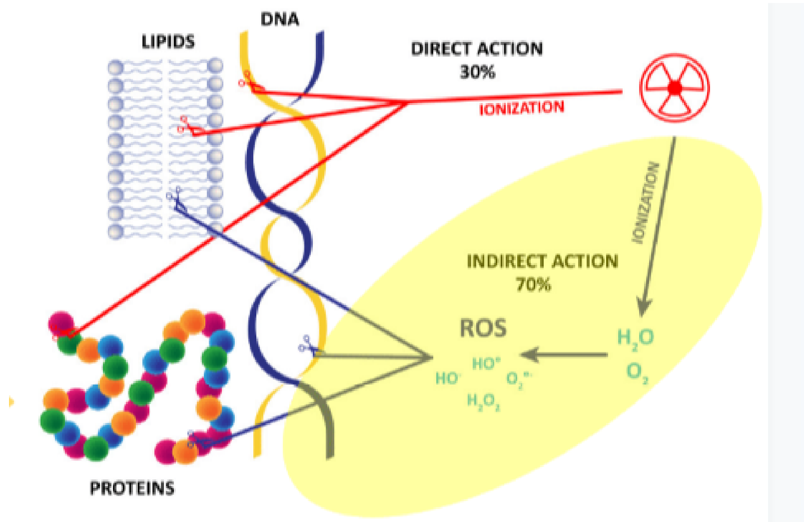


Fig. 6. Quantification of metastasis in lung shown in Fig. 5. The difference between the lungs of mice irradiated with FLASH (yellow bar) and conventional dose-rate (red bar) is statistically significant ($p < 0.05$).

Biological mechanisms at UHDR?





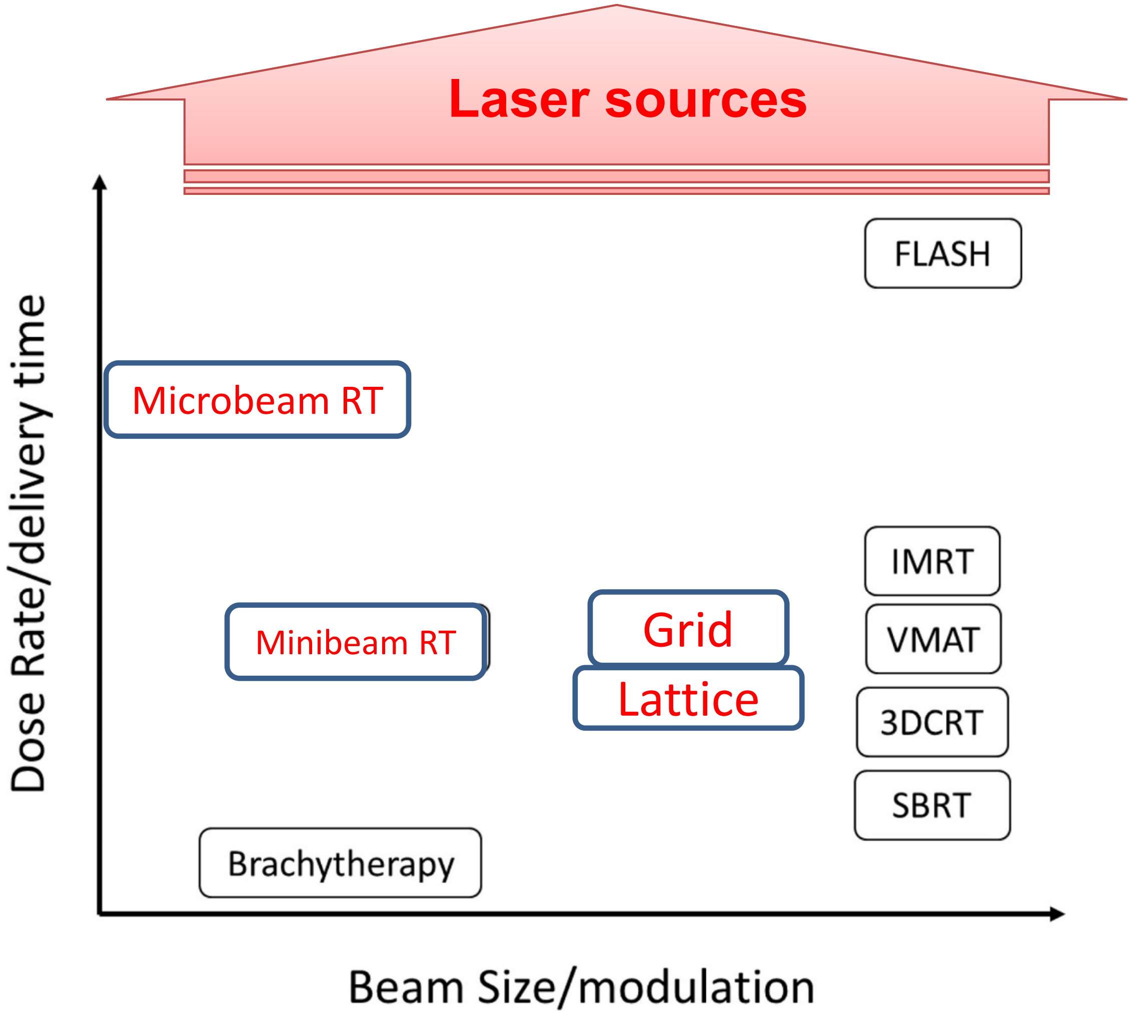


- Direct DNA damage, standard paradigm for radiation effects
- Lack of understanding of biological response at Ultra-high dose-rate
- Bespoke research infrastructure required

From Vozenin, Spitz, Limoli

Spatial and temporal dependency of radiation action

- Future radiotherapies have multiple options for spatial and temporal delivery schedules
- Most offer differential protection of normal tissue
- The biological rationale is not clear
- The impact of increased dose-rate is unclear
- LhARA will be able to test the interrelationship between temporal and spatial effects for different ion species



Griffin *et al.*, History and current perspectives on the biological effects of high-dose spatial fractionation and high dose-rate approaches: GRID, Microbeam & FLASH radiotherapy. *Br J Radiol*. 2020 Sep 1;93(1113):20200217

Summary

- lhARA will provide a unique UK platform for Radiobiology studies of laser driven ions and photons:
  - Validating the **future applications** of laser driven sources
  - Testing largely **unexplored regimes** of ultra-high dose rates
  - Validating new understanding of **dose-rate effects**
- With the development and optimization of beam production and delivery techniques **more energetic** ion beams and species will be available.
- A range of dose-rates are possible including well beyond the FLASH range where **physical, chemical and biology knowledge is limited**.
- To properly understand ultra-high dose-rate radiobiology more comparisons are needed at similar energies with conventional ions and photon sources across a range of dose-rates and biological models.