# Laser-driven ion sources and ultra-high dose rate radiobiology

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QUEEN'S UNIVERSITY BELFAST

FRPT
FLASH RADIOTHERAPY & PARTICLE THERAPY 2021

A-SAIL
ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS

EPSRC
Pioneering research and skills

# Faculty Disclosure

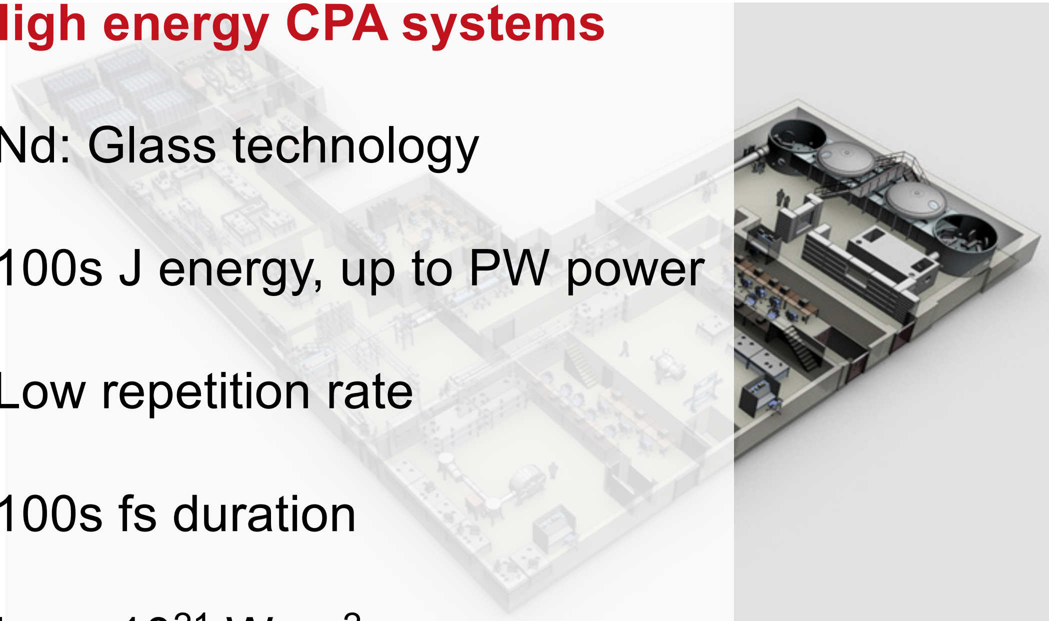
| | |
|---|---|
| X | No, nothing to disclose |

# Outline

- Laser-driven acceleration
- Proton acceleration (TNSA mechanism)
- UHDR radiobiology
- Carbon acceleration (RPA)
- Irradiation set-up and dosimetry
- Examples of *in-vitro* investigations

# Two main classes of lasers for ion acceleration

## High energy CPA systems



•Nd: Glass technology

•100s J energy, up to PW power

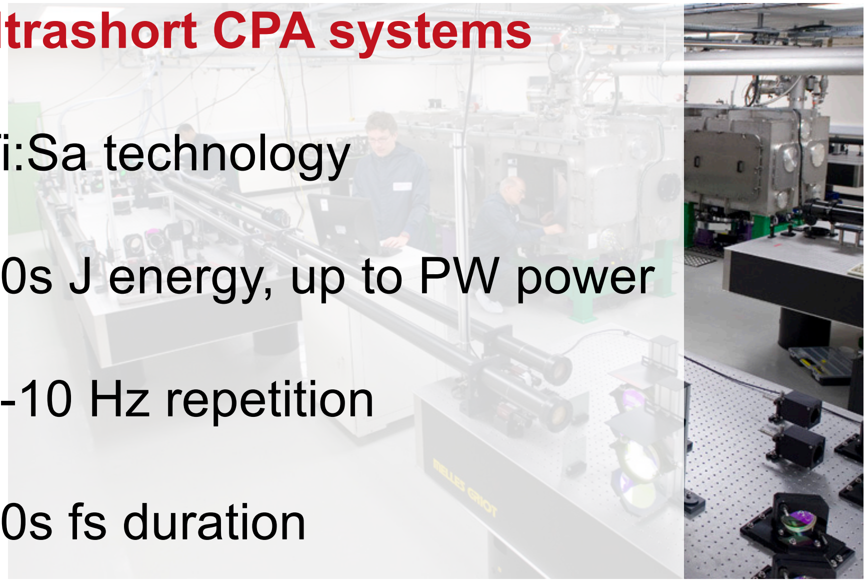
•Low repetition rate

•100s fs duration

•$I_{max}$~ $10^{21}$ $Wcm^2$

**VULCAN, RAL (UK)**
Phelix, GSI (De)
Trident, LANL (US)
Texas PW, Austin (US)
.....

## Ultrashort CPA systems



•Ti:Sa technology

•10s J energy, up to PW power

•1-10 Hz repetition

•10s fs duration

• $I_{max}$~ $10^{21}$ $Wcm^2$

**GEMINI, RAL (UK)**
Draco, HZDR (De)
Pulser I, APRI (Kr)
J-Karen, JAEA (J)
.....

# Extreme energy confinement in space and time leads to extreme conditions

*$I \sim 5\ 10^{20}\ W/cm^2$*

***Electric field***

$$E = \sqrt{4\pi \frac{I}{c}} = 3 \cdot 10^{13} V/m \sim 50 \frac{e}{r_b^2}$$

**Ultrafast ionization and plasma production**

***Electron momentum***

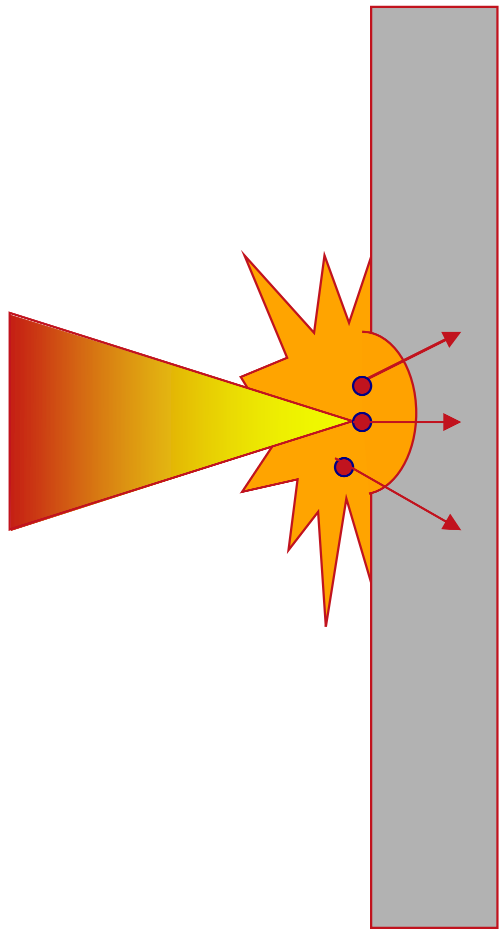
$$p_{osc} = \frac{eE}{\omega} = 8.5 m_e c$$

**Heating of electrons to relativistic energies**

***Radiation Pressure***

$$P_{rad} = \frac{I}{c} \sim 30 Gbar$$

***Ultrastrong pressure applied to the target surface***



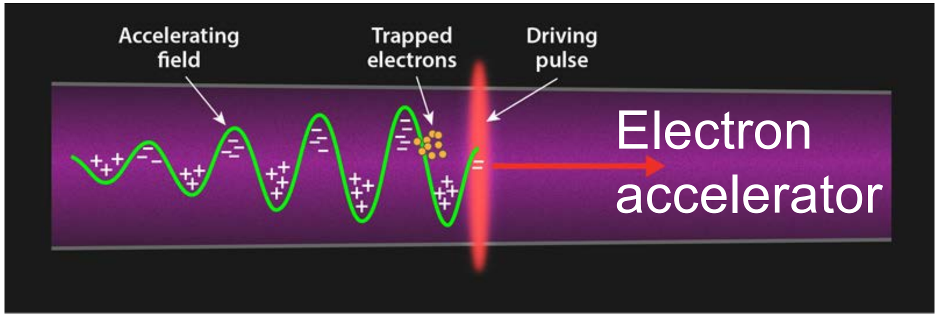
# Laser-acceleration of particles

Plasma can support very large E-fields (up to $10^{12}$ V/m = TV/m) via local charge separation initiated by the laser pulse

Cf: in RF accelerators (cyclotron/LINAC)

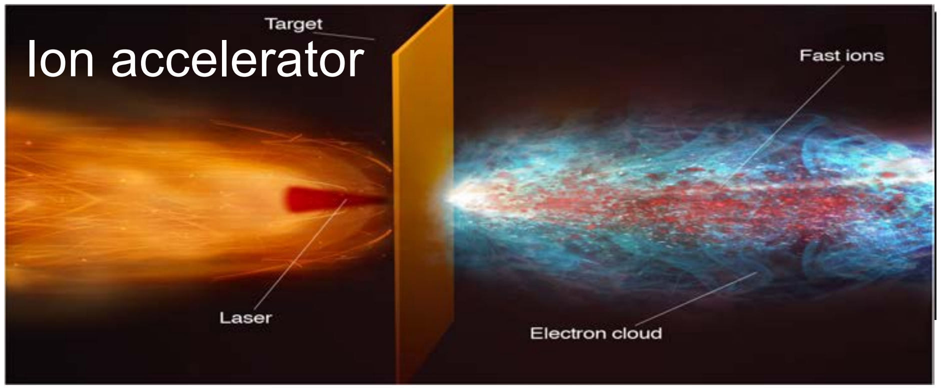
$E_{max}$ ~ 50 MV/m

**Very short acceleration distances**: compact accelerators

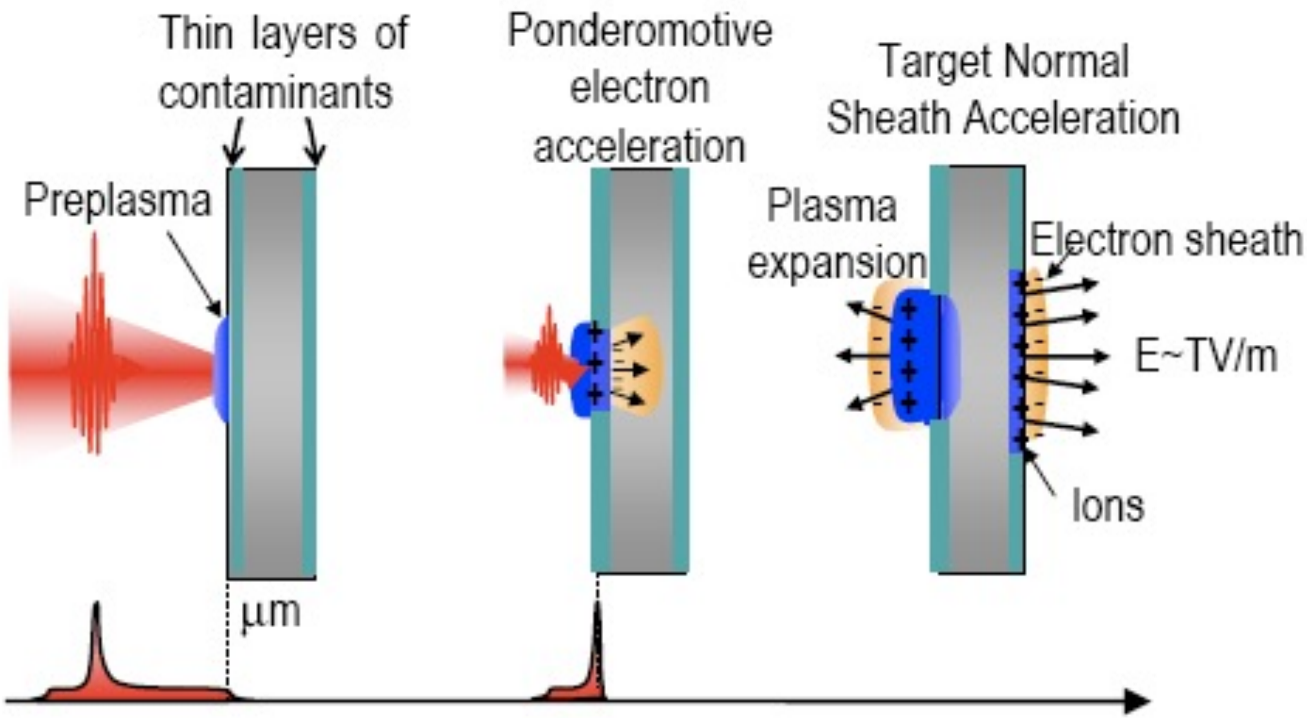



**Ultrashort particle sources:** femtosecond/picosecond duration

**Very bright sources:** Significant dose delivery



# Proton accelerators: sheath acceleration from surface layers




Investigated since ~2000

TNSA (Target Normal Sheath Acceleration)

$$E_{acc} = \sqrt{\frac{n_h K T_h}{\varepsilon_0}}$$

scales with laser intensity/energy

$E_{ions} \sim I^{0.5-1}$

Review:

Macchi, Borghesi, Passoni, Rev. Mod. Physics, **85**, 751 (2013)

# Properties of TNSA proton beams

## Short duration at source:

bursts with duration ~ ps

## Broad spectrum:

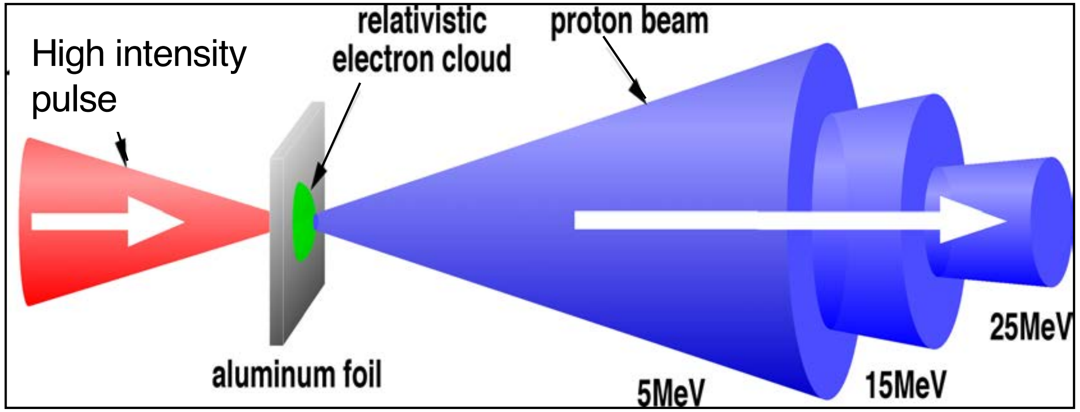
continuum up to 10s of MeV
in a divergent beam
$E_{max}$ ~ 85 -100 MeV

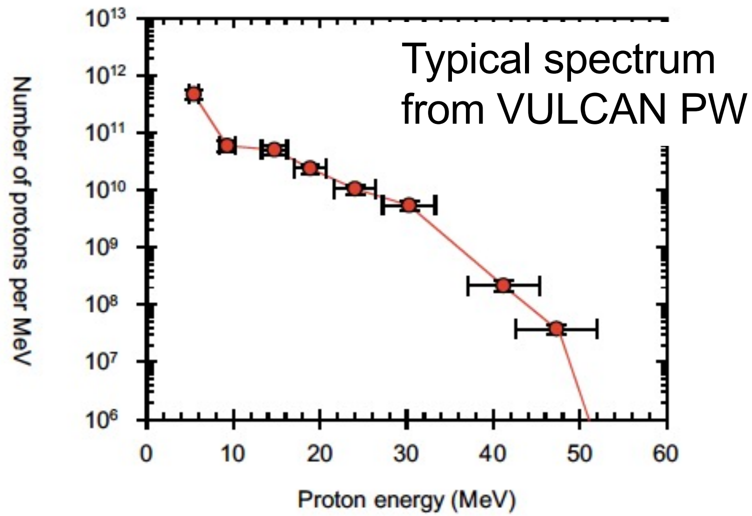
## High laminarity:

rms emittance < 0.01 $\pi$ mm-mrad

## High brightness:

$10^{11}$ – $10^{13}$ protons/ions per shot

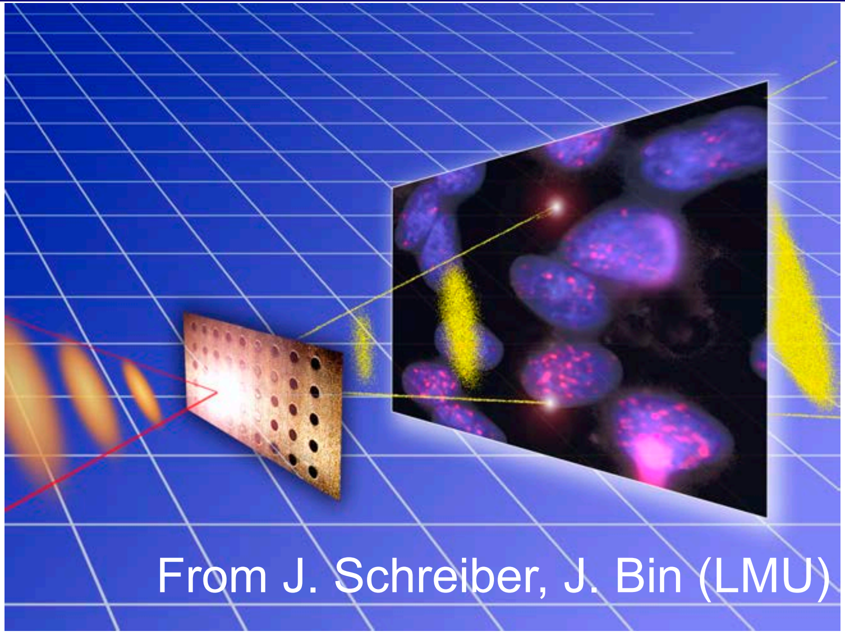


# Application to radiobiology

Studies since ~ 2010 @

- **APRC, JAEA (Japan)**
- **HZDR (Germany)**
- **LMU/MPQ (Germany)**
- **QUB/A-SAIL (UK)**
- **LOA/LULI (France)**
- **….**




**Motivations**:

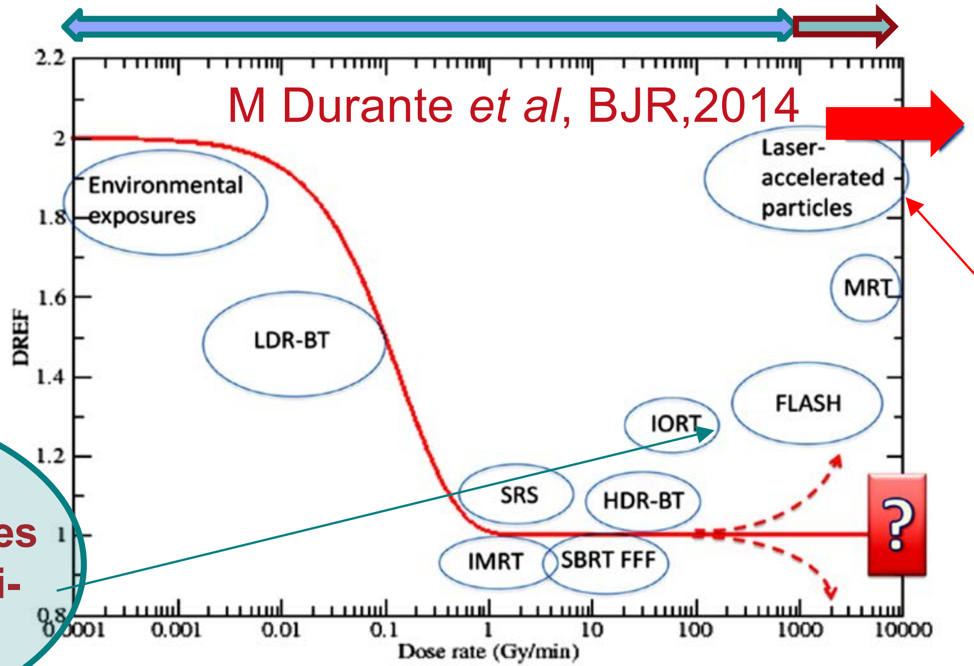
1. Development of a methodology and demonstration of viability
2. Validation of laser-driven sources in view of future therapeutic use
3. Assessment of any anomaly related to the ultrashort delivery
4. Extension of FLASH studies to higher dose-rate regimes

# Radiobiology at Ultra-High Dose Rate

**Conventional dose-rate**
0.01-0.1 Gy/s (1-10 Gy/min)

**FLASH dose-rate**
>40 Gy/s (>2400 Gy/min)

**Laser-driven dose-rate**
$>10^9$ Gy/s ($>10^{11}$ Gy/min)




**Possible effects**

- Spatio-temporal overlap of independent tracks
- Local depletion of oxygen
- Potential commonalities with **FLASH effects**

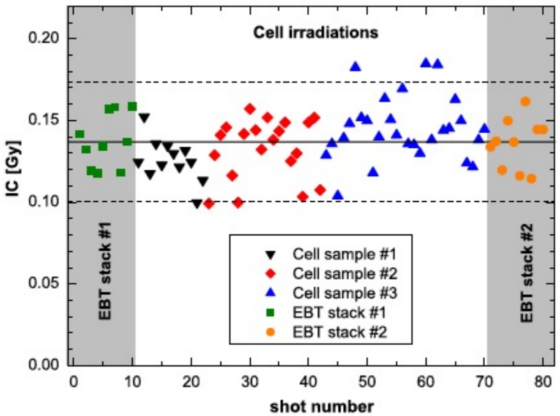
**Spare normal tissues preserving the anti-tumor activity**

**A Novel regime of radiobiology**

Recent review: Chaudhary P, et al (2021), *Front. Phys.* **9**:624963.

# Two different approaches to laser-driven experiments

1. Multi-shot: Required dose is delivered in several fractions

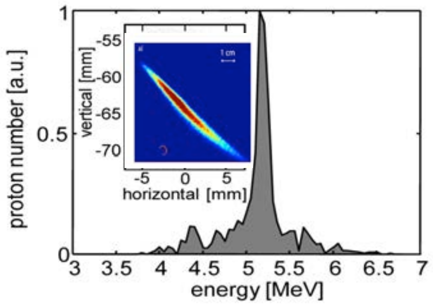



High-rep system
High-rep target
Typically Ti:Sa, fs systems
Dose control, transport

***Pulse dose-rate***: UHDR
***Mean dose-rate***:
conventional (Gy/min)

e.g. S. Kraft et al, NJP (2010)
A. Yogo, et al, APL(2011)
E. Bayart et al, Sci. Rep (2019)

2. Single shot irradiation: deliver of a single dose at Gy level in ~ 100s ps - ns pulses




Suited to low rep systems

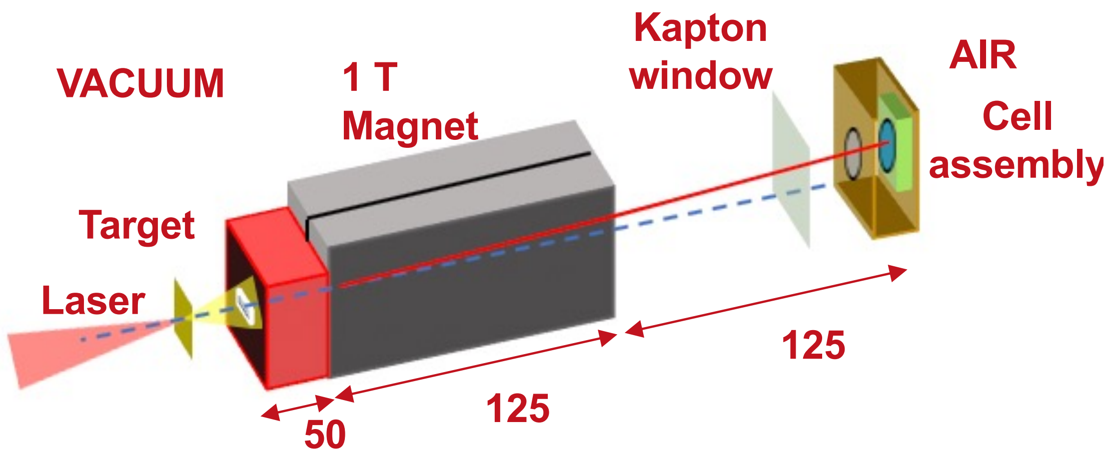
**Pulse DR = Mean DR = UHDR**

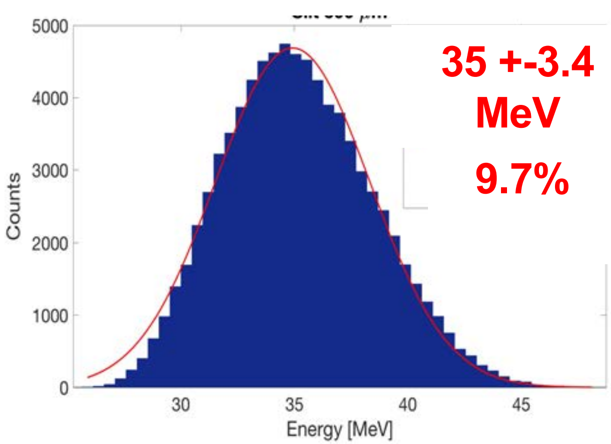
*e.g.* *J*. Bin *et al*., Appl. Phys. Lett. (2012)
D. Doria *et al*, AIP advances (2012)

# Single-shot experimental arrangement for UHDR beam delivery

**Compact and simple setup**

- Multi-GY dose **in a single shot**
- High energy resolution at the cell position
- High dose-rate at the cell plane
- Easy implementation in physics research lab



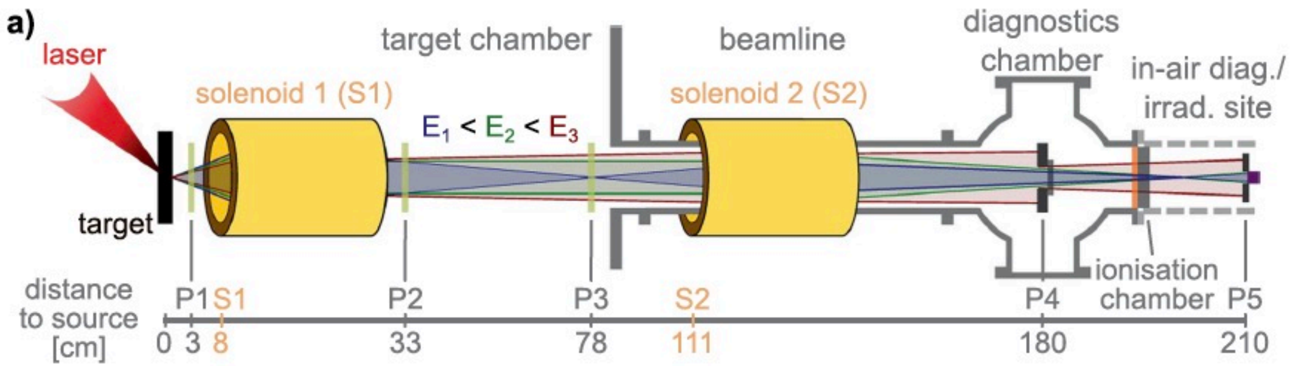

VULCAN PW:
Energy distribution at cell location (35 MeV)

Proton pulse **duration** on cells: ΔT~ 350 ps

**Dose** ~ 2 Gy

**Dose-rate** ~ 6 $10^9$ Gy/s

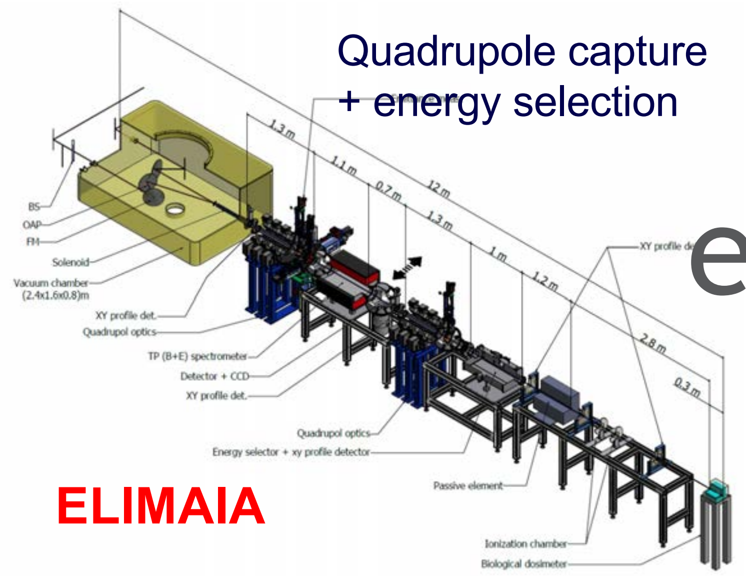
# Advanced delivery systems




HZDR

F.E. Brack *et al*,
Sci. Reports (2020)

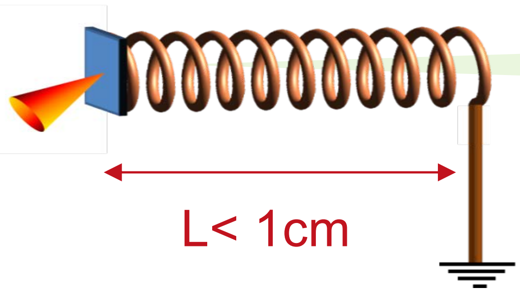
See talk by Brack
(today at 3.20)



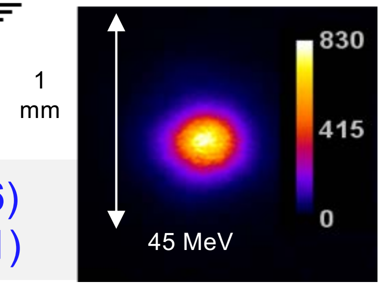

eli beamlines

INFN

QUEEN'S UNIVERSITY BELFAST




**Miniature structures** for
beam transport/conditioning




S. Kar *et al*, Nature Comm. (2016)
H. Ahmed *et al*, Sci. Report (2021)

# Acceleration of carbon ions employs more advanced acceleration schemes

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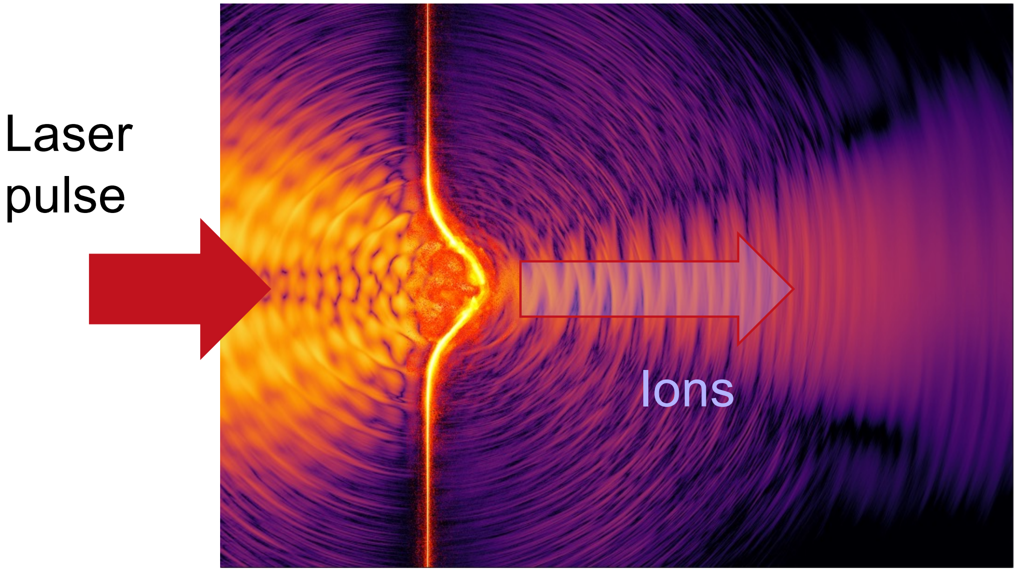
ADVANCED STRATEGIES FOR ACCELERATING IONS WITH LASERS




**Radiation pressure acceleration** of ultrathin foils (~ 10 nm)

## Interest of carbon ions

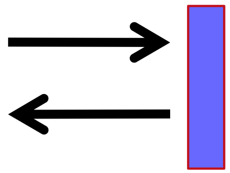
- ✓ More complex damages to the cell DNA
- ✓ Higher LET > 100 KeV/um
- ✓ Higher RBE
- ✓ Higher efficiency for the treatment of radioresistent tumours
- ✓ Growing interest in HI-FLASH

*(see talk by M. Durante)*

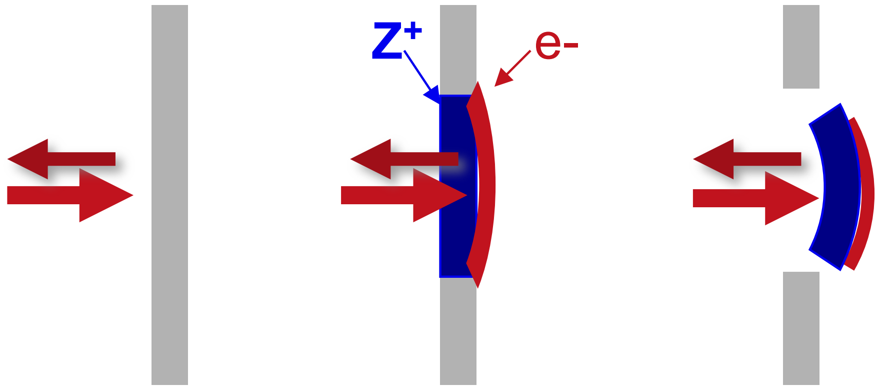
# Ultrathin foils – Radiation Pressure Acceleration

**Radiation pressure upon light reflection from a mirror surface:**

$$p_R = \frac{2I_L}{c}$$



$P_L$=60 Gbar
@ $10^{20}$Wcm$^{-2}$




Most efficient with ultrathin foils (nm-scale) –
***Light Sail*** RPA

- **Bulk acceleration mechanism**
- **Fast scaling with intensity**

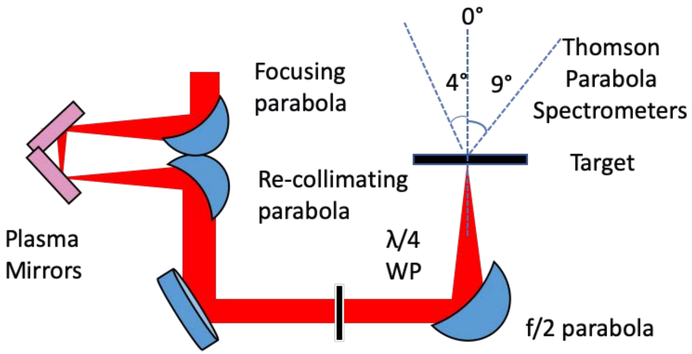
Target **must stay opaque**:

Potential issues ⇒ Electron heating
Target disassembly
Transverse instabilities

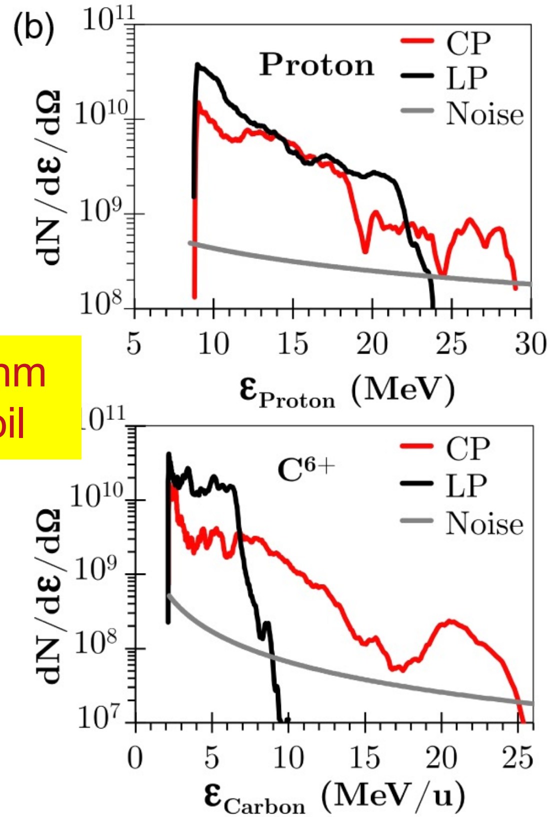
**Experimental requirements**:
- Ultrashort pulses
- Temporal "cleaning"
- Circular polarization

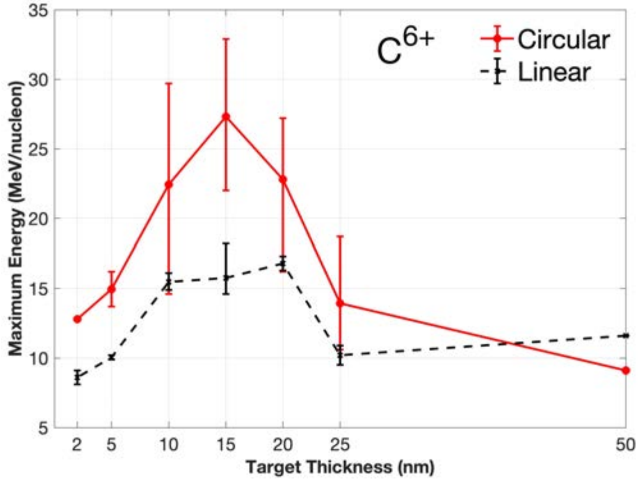
# Experiments with ultrathin foils – efficient Carbon acceleration

C. Scullion et al, PRL, **119**, 054801 (2018)
A. McIlvenny et al, PRL, 127, 194801 (2021)




10 nm C foil




GEMINI: 40 fs, 6 J, ~ 5 $10^{20}$ W/cm$^2$, plasma mirror for contrast enhancement, polarization control

Optimum target thickness for Carbon acceleration

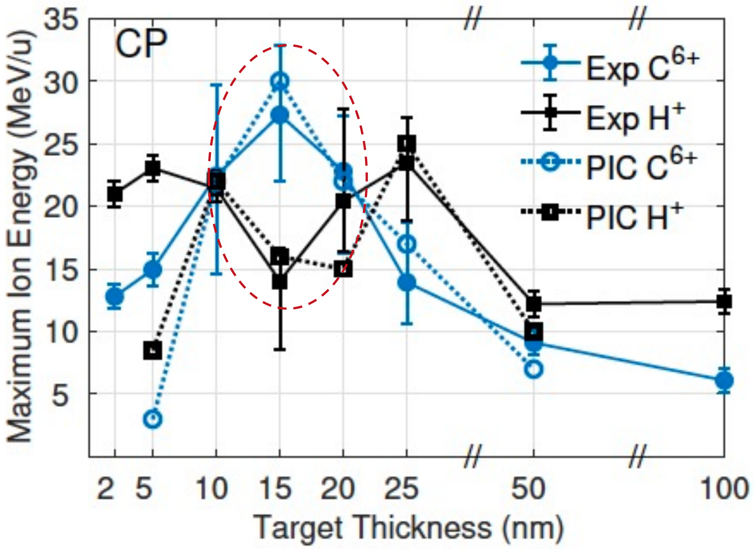
Optimum thickness for LS-RPA:

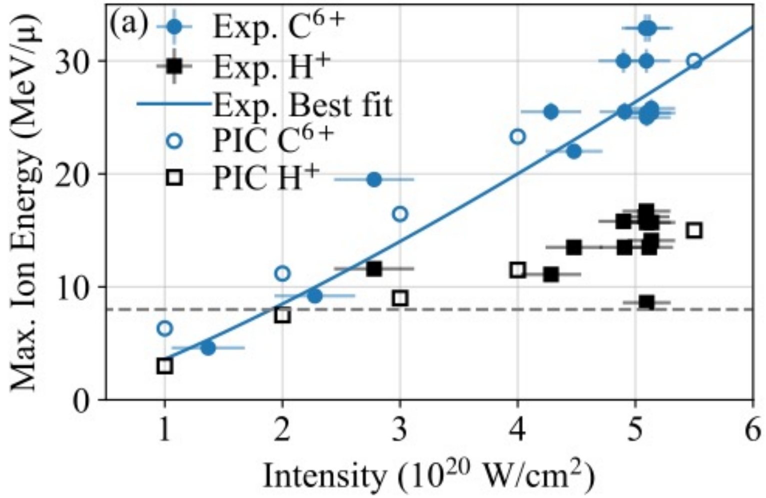
$$\eta \approx \pi \frac{n_0}{n_c}\frac{\ell}{\lambda} \sim a_0$$

- **Strong dependence on polarization, onset of Light Sail acceleration**
- **Existence of an intensity dependence, optimum target thickness**

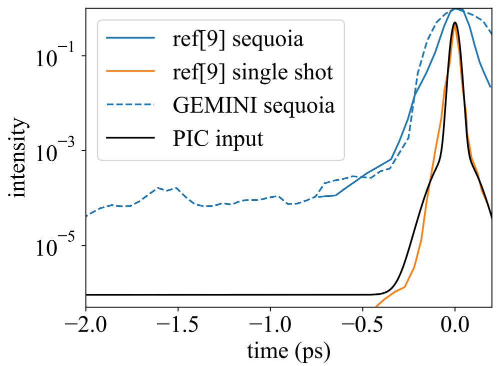
# "Proton-free" high- energy carbon beams

A. McIlvenny *et al*, PRL, **127**, 194801 (2021)



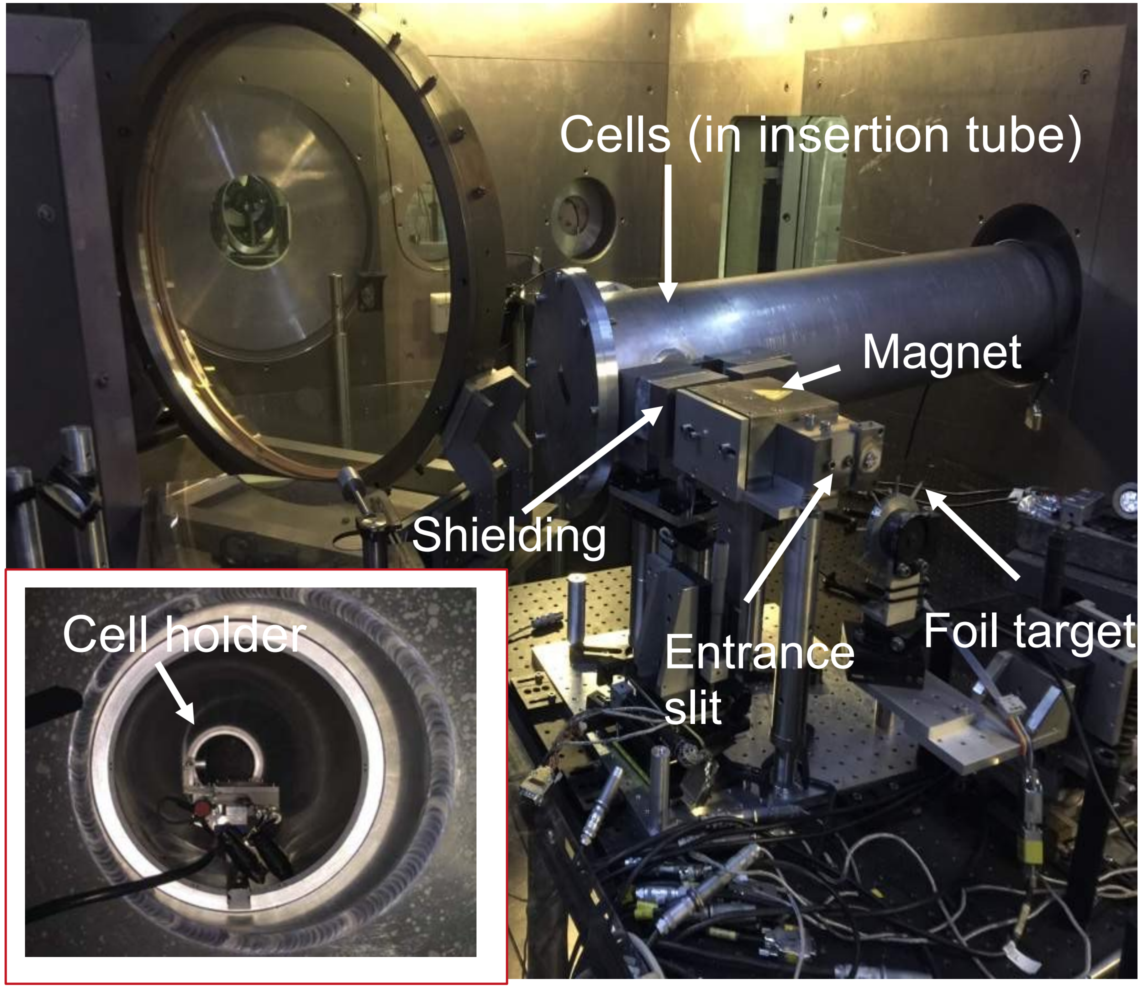

At the optimum thickness, precursor energy leads to pre-expansion of protons, which are not accelerated efficiently.



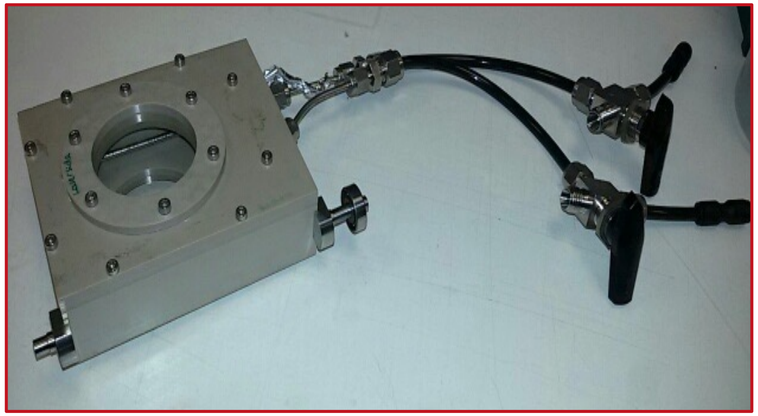

Modelling the laser rising edge on ps time scales is key to understanding the different species dynamics

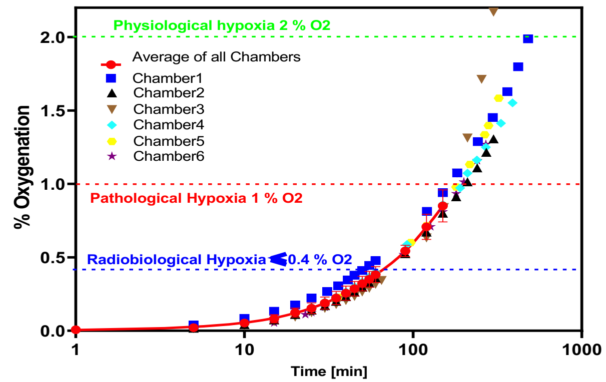
Possibility of **pure Carbon** acceleration at high energy

# Example: irradiation set-up @ VULCAN PW RAL




## Hypoxia chamber

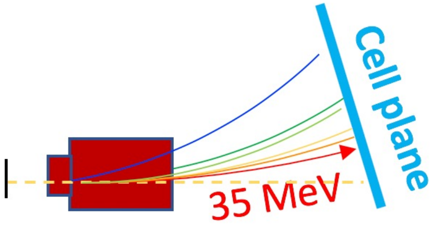




# Cell irradiation and dosimetry

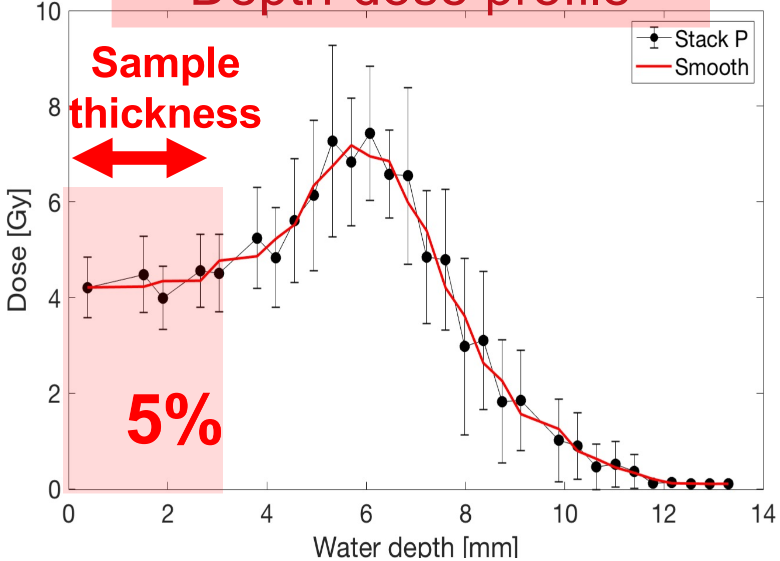
UNPUBLISHED DATA-DO NOT COPY OR DISTRIBUTE

See talk by G. Milluzzo (today at 3.30)



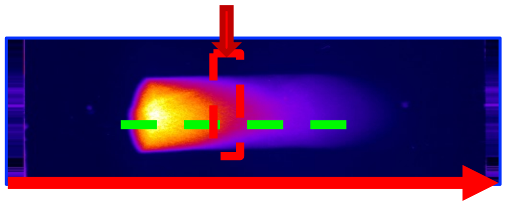

**Protons @VULCAN**

Depth-dose profile



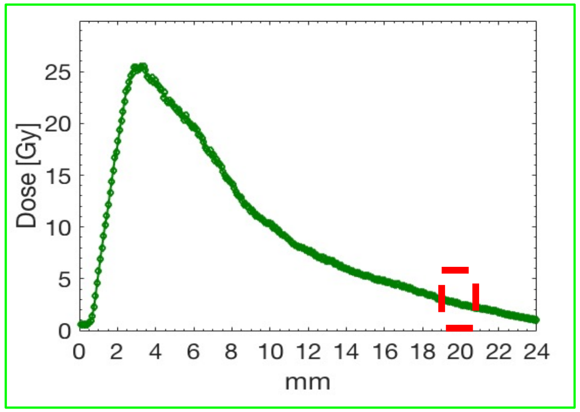

**Dose distribution with RCF @ cell plane**

**Tube position**



**Low energy** **35 MeV** **High energy**

**0.5-30 Gy whole energy spectrum**

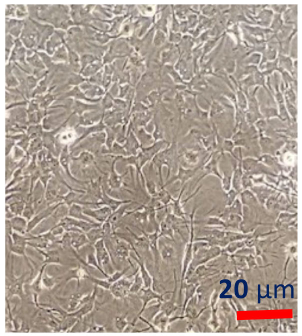


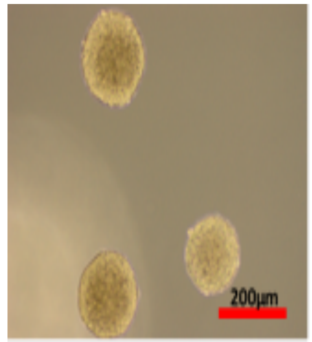

Main cell models:
**AG10522** (normal, 2D)

**GBM stem cells**
(cancerous, 2D and 3D)

2D monolayers

**3D** neurospheres



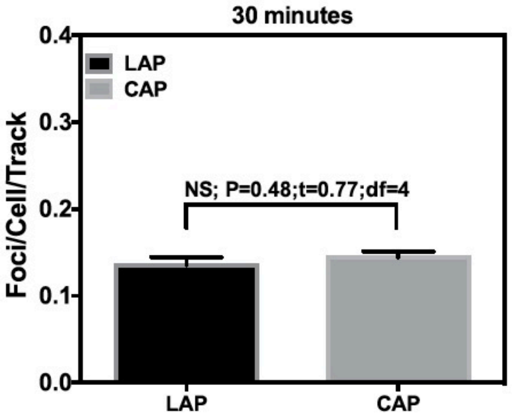



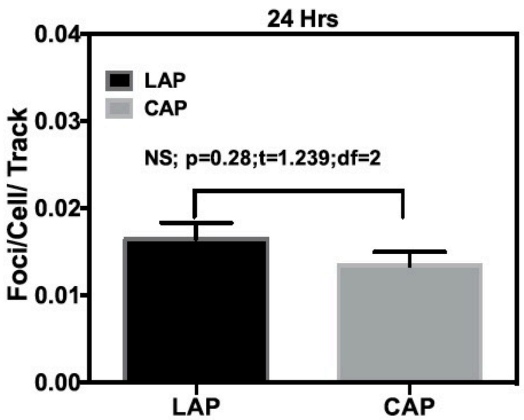
# UHDR effects?

DNA damage studies

Normal cells (AG01522, 2D)

Oxic conditions, 10 MeV UHDR protons



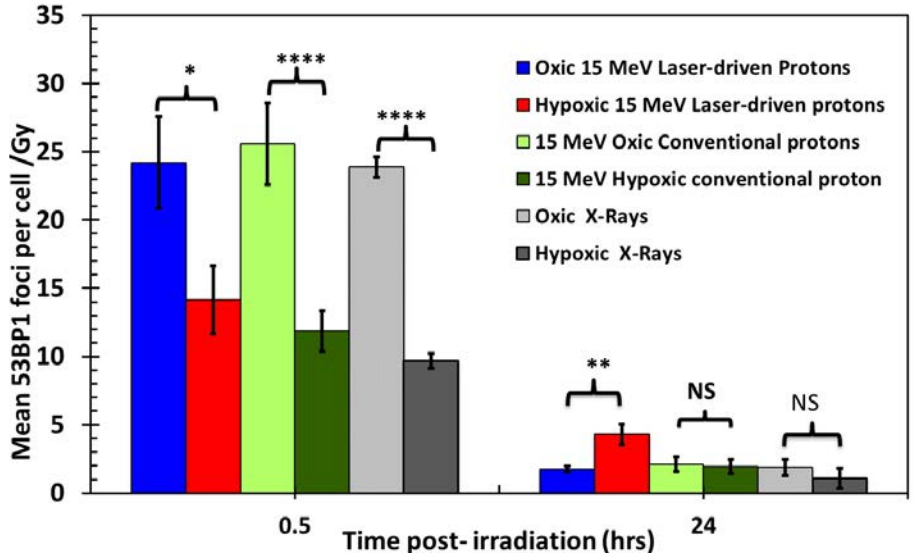

Conventional irradiations at LNS-INFN (Italy)

No differences between UHDR and *conventional* DR

Consistent with all previous work at ~Gy dose level + oxic conditions

F. Hanton *et al*, Sci. Report, **9**, 4471 (2019)

Hypoxic measurements (15 MeV)




UHDR more damaging @ 24 hours

P. Chaudhary et al , BMC Radiation Oncology, under revision (2021)

# UHDR proton vs carbon

DNA damage studies

P. Chaudhary et al, in preparation (2021)

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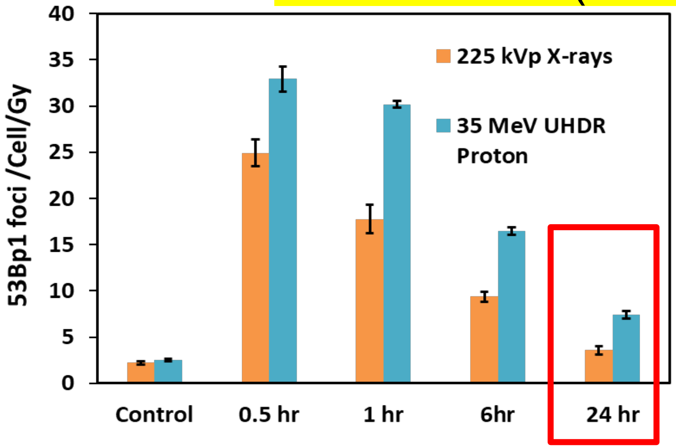
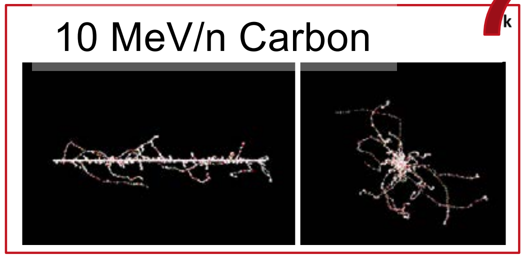
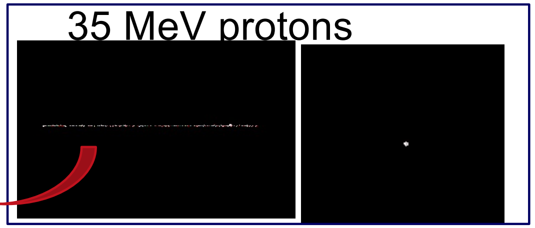
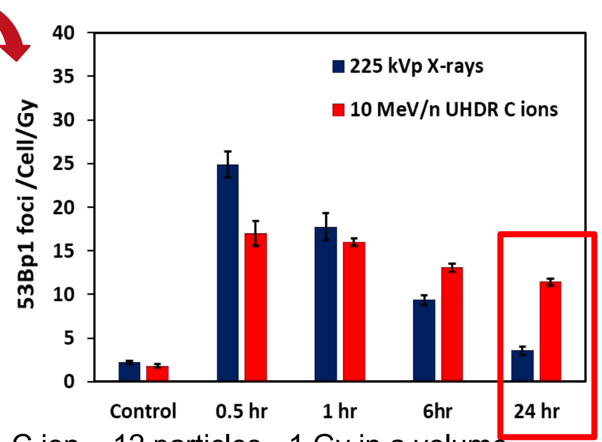
Cancer cells (GBM E2, 2D)

See talk by P. Chaudhary (today at 3.50)



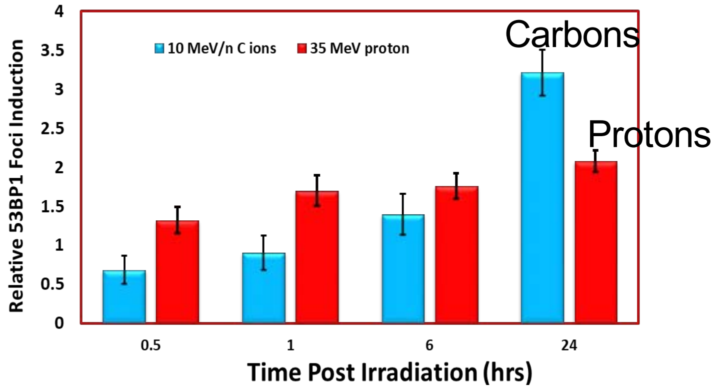




p+ - 1190 particles for 1 Gy in a volume of 10 µm Radius with 5 µm length

C ion – 12 particles - 1 Gy in a volume of 10µm Radius with 5 µm length

RFI = Avg. 53BP1 foci count induced by ions / Avg. 53BP1 foci induced by X rays

Carbon show, as expected, more complex DSB DNA damage




Need comparator, carbon data at conventional DR to assess any UHDR effects

# Conclusions

## Laser-driven ion sources and ultra-high dose rate radiobiology

**Laser-driven ion acceleration**:

- radically different technology
- Intrinsically short bursts, high flux
- Proton + carbon sources

**UHDR radiobiology**

Compact set-up
Multi-Gy doses, $>10^9$ Gy/s
Extension of FLASH regimes

Emerging evidence of non-standard cell response at UHDR
Need for new models and new understanding

# Main contributors and sponsors

**P. Chaudhary**, S.Kar, F.Hanton, D. Gwynne, C. Majorino, **A. McIlvenny**, **B Odlizilik**, C. Scullion, A.McMurray, K. Polin, S. McCallum, **K.Prise,** *Queen's University Belfast*

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**G.Milluzzo**, F. Romano, G.A.P.Cirrone LNS, INFN (Italy)

A. Macchi, Istituto Nazionale di Ottica, CNR (Italy)

P.McKenna (Strathclyde Univ ) , Z. Najmudin (Imperial College) +…

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